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14

Anesthesia and Analgesia

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Journal of the International Anesthesia Research Society
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In

Reversal

of nondepolarizing
muscle relaxants,
don't look for what's better...
...look for what's best

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(pyridostigmine
bromide injection, USP)
when compared to neostigmine

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  2) Salivation
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Regonol (pyridostigmine bromide injection, USP)

BRIEF SUMMARY—(Please consult full package insert, enclosed in every package, before using Regonol)

INDICATIONS—Pyridostigmine bromide is useful as a reversal agent or antagonist to nondepolarizing muscle relaxants.

CONTRAINDICATIONS—Known hypersensitivity to anticholinesterase agents; intestinal and urinary obstructions of mechanical type.

WARNINGS—Pyridostigmine bromide should be used with particular caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine should also be used with caution in patients with cardiac dysrhythmias. When large doses of pyridostigmine bromide are administered, as during reversal of muscle relaxants, prior or simultaneous injection of atropine sulfate is advisable. Because of the possibility of hypersensitivity in an occasional patient, atropine and anti-shock medication should always be readily available.

When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

Use in Pregnancy—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

ADVERSE REACTIONS—The side effects of pyridostigmine bromide are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

DOSAGE AND ADMINISTRATION—When pyridostigmine bromide is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg) or glycopyrrolate in equipotent doses be given intravenously immediately prior to or simultaneous with its administration. Side effects, notably excessive secretions and bradycardia, are thereby minimized. Reversal dosages range from 0.1-0.25 mg./kg. Usually 10 or 20 mg. of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur, e.g., in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether. Under these circumstances ventilation must be supported by artificial means until the patient has resumed control of his respiration.

HOW SUPPLIED—Regonol is available in:
5 mg./ml.: 2 ml. ampuls—boxes of 25—NDC-0052-0460-02
5 ml. vials—boxes of 25—NDC-0052-0460-05

REFERENCES:
1. Gyermek L: Clinical studies on the reversal of the neuromuscular blockade produced by pancuronium bromide. I. The effects of glycopyrrolate and pyridostigmine. *Curr Ther Res* 18:377-386, 1975.
2. Ravin MB: Pyridostigmine as an antagonist of d-tubocuranrine-induced and pancuronium-induced neuromuscular blockade. *Anesth Analg—Curr Res* 54:317-321, 1975.

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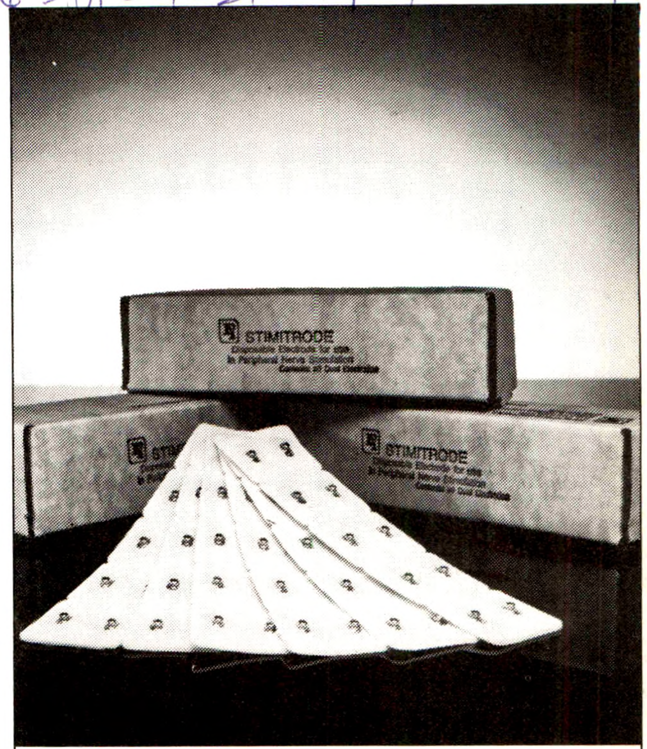

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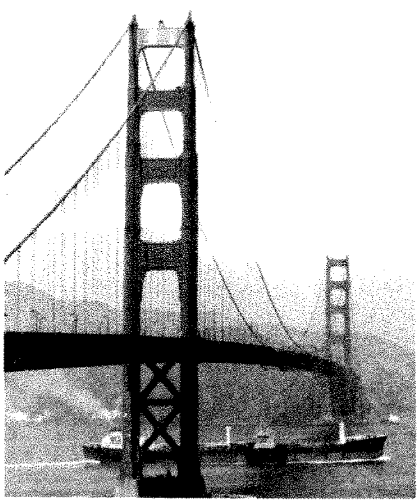
THE SUFENTA® REPORT

A PRACTICAL ANESTHESIA UPDATE

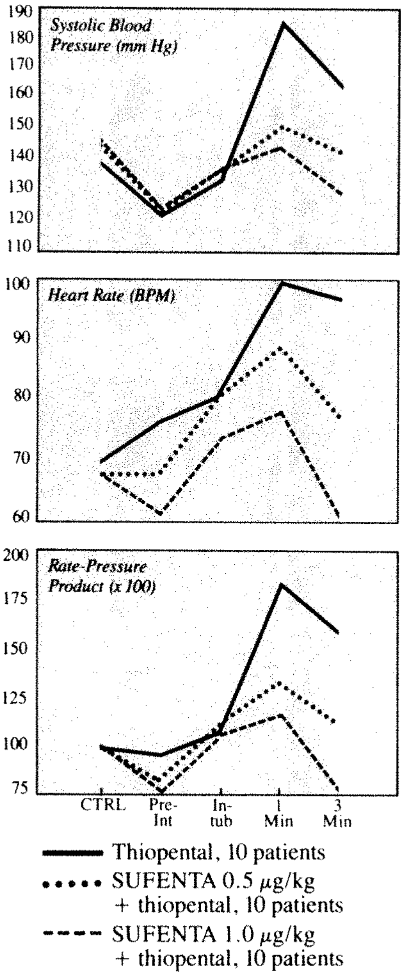
VOL. 1, NO. 1 JANSSEN PHARMACEUTICA INC. WINTER 1986

LESS BARBITURATE, BETTER STABILITY WITH LOW-DOSE SUFENTA®

SAN FRANCISCO: Low doses of SUFENTA® (sufentanil citrate) Injection Ⓒ, given prior to thiopental as an adjunct to induction, improved hemodynamic stability and reduced barbiturate requirements, according to a study presented here at the 1985 Annual Meeting of the A.S.A. In a group of 30 adult patients who underwent surgery of 25 min. to 8.5 hr. duration, thiopental was used for induction, either alone or combined with SUFENTA. SUFENTA (0.5 or 1.0 μg/kg) reduced thiopental requirements by 50% to 68%, respectively, and the hemodynamic response to laryngoscopy and intubation was attenuated, as measured by systolic pressure, heart rate and rate-pressure product. Bradycardia, truncal rigidity and recall were not observed.



Better Hemodynamic Control



(Abstracted from Brizgys, Morales and Owens, *Anesthesiology* 1985; 63:A377)

Experience With 93 Patients Generates "Thumbnail" Dosage Guidelines

Clinical experience with SUFENTA in general surgery revealed that *total dosage requirements averaged about 1 μg/kg/hour or less*, in surgery up to 8 hours.

In the same patients the *induction dose averaged about 75% of total dose*. The remainder was given in incremental maintenance doses as needed.

The induction dose of SUFENTA administered prior to intubation reduces hypertension and tachycardia.

In every case, however, dosage should be titrated to individual patient needs.

NOW SHOWING: AN INFORMATIVE 22-MINUTE FILM

Benjamin J. Kripke, MD, and Edson O. Parker III, MD, are featured in the medical film "SUFENTA: A Practical Guide for General Surgical Procedures." The anesthesiologists demonstrate, through actual hands-on experience, how careful dosage planning provides maximal hemodynamic stability throughout the entire procedure. To arrange a viewing of this film please contact your local Janssen Representative.

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Adult Dosage Recommendations: A Summary

Please see full Prescribing Information, including dosage, on next page.

	General Surgical Procedures	Major Surgical Procedures
Expected Duration	1 to 2 hours	2 to 8 hours
Types of Procedures	Total vaginal hysterectomy, gall bladder surgery, bilateral inguinal hernia repair, open reduction of fractures	Major orthopedic surgery, carotid endarterectomy, nephrectomy, major abdominal surgery (e.g., colectomy)
Recommended Induction Dose	1 to 1.5 μg/kg (1.4 to 2.1 ml for a 70 kg patient), administered with N_2O/O_2, endotracheal intubation and mechanical ventilation	1 to 5 μg/kg (1.4 to 7 ml for a 70 kg patient), administered with N_2O/O_2, endotracheal intubation and mechanical ventilation
Recommended Maintenance Dose	10 to 25 μg (0.2 to 0.5 ml) based upon changes in clinical signs and patient's response to initial dose	10 to 25 μg (0.2 to 0.5 ml) based upon changes in clinical signs and patient's response to initial dose
Total Dosage	For cases lasting 2 hours, would not be expected to exceed 2 μg/kg (2.8 ml for a 70 kg patient) when used with N_2O/O_2	For cases lasting 8 hours, would not be expected to exceed 8 μg/kg (11.2 ml for a 70 kg patient) when used with N_2O/O_2

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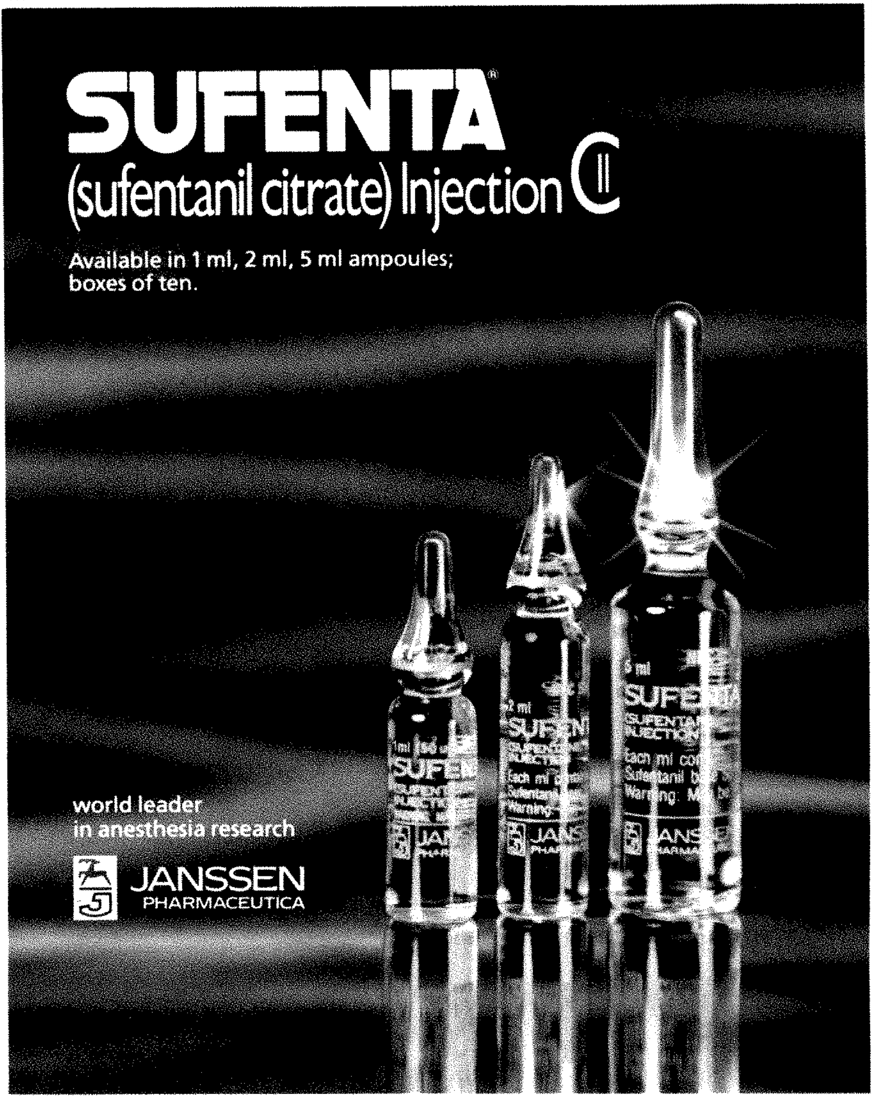
In actual clinical practice, when used in balanced general anesthesia, SUFENTA is about 10 times as potent as fentanyl. Thus, 1 ml SUFENTA (50 μg/ml) is equivalent to 10 ml fentanyl (50 μg/ml).

Because of this potency difference, less volume of drug is needed, making it especially convenient for use in cardiovascular surgery and longer procedures. For accurate dosage calibration in shorter procedures, a tuberculin syringe, a 2 ml insulin syringe or dilution may be helpful.

In a laboratory study, SUFENTA has been found to be compatible nd stable in solution with 5% lucose in water, 5% glucose in rmal saline, lactated Ringer's lution and normal saline (tested plastic containers refrigerated 4°-8°C for 24 hours followed 48 hours at room temperature).



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DESCRIPTION: SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.

CLINICAL PHARMACOLOGY: SUFENTA is an opioid analgesic. When used in balanced general anesthesia, SUFENTA has been reported to be as much as 10 times as potent as fentanyl. When administered as a primary anesthetic agent with 100% oxygen, SUFENTA is approximately 5 to 7 times as potent as fentanyl. (See dosage chart for more complete information on the use of SUFENTA.) At doses of up to 8 µg/kg, SUFENTA provides profound analgesia; at doses ≥8 µg/kg, SUFENTA produces a deep level of anesthesia. SUFENTA produces a dose related attenuation of catecholamine release, particularly norepinephrine.

The pharmacokinetics of SUFENTA can be described as a three-compartment model, with a distribution time of 1.4 minutes, redistribution of 17.1 minutes and an elimination half-life of 164 minutes. The liver and small intestine are the major sites of biotransformation. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug. Plasma protein binding of SUFENTA is approximately 92.5%.

SUFENTA has an immediate onset of action, with relatively limited accumulation. Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with equipotent dosages of fentanyl. At dosages of SUFENTA of 1-2 µg/kg, recovery times are comparable to those observed with fentanyl; at dosages of >2-6 µg/kg, recovery times are comparable to enflurane, isoflurane and fentanyl. Within the anesthetic dosage range of 8-30 µg/kg of SUFENTA, recovery times are more rapid compared to equipotent fentanyl dosages.

At dosages of ≥8 µg/kg, SUFENTA produces hypnosis and anesthesia without the use of additional anesthetic agents. A deep level of anesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to 25 µg/kg attenuate the sympathetic response to surgical stress. The catecholamine response, particularly norepinephrine, is further attenuated at doses of SUFENTA of 25-30 µg/kg, with hemodynamic stability and preservation of favorable myocardial oxygen balance.

The vagolytic effects of pancuronium may produce a dose dependent elevation in heart rate during SUFENTA-oxygen anesthesia. The vagolytic effect of pancuronium may be reduced in patients administered nitrous oxide with SUFENTA. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent may be used to maintain a stable lower heart rate and blood pressure during SUFENTA-oxygen anesthesia.

Preliminary data suggest that in patients administered high doses of SUFENTA, initial dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane.

Bradycardia is infrequently seen in patients administered SUFENTA-oxygen anesthesia. The use of nitrous oxide with high doses of SUFENTA may decrease mean arterial pressure, heart rate and cardiac output.

Assays of histamine in patients administered SUFENTA have shown no elevation in plasma histamine levels and no indication of histamine release.

SUFENTA at 20 µg/kg has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anesthesia supplementation in one study of patients undergoing craniotomy. During carotid endarterectomy, SUFENTA-nitrous oxide/oxygen produced reductions in cerebral blood flow comparable to those of enflurane-nitrous oxide/oxygen. During cardiovascular surgery, SUFENTA-oxygen produced EEG patterns similar to fentanyl-oxygen; these EEG changes were judged to be compatible with adequate general anesthesia.

The intraoperative use of SUFENTA at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. The incidence of postoperative hypertension, need for vasoactive agents and requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of SUFENTA as compared to patients given inhalation agents.

Skeletal muscle rigidity is related to the dose and speed of administration of SUFENTA. This muscular rigidity may occur unless preventative measures are taken (see Warnings).

Decreased respiratory drive and increased airway resistance occur with SUFENTA. The duration and degree of respiratory depression are dose related when SUFENTA is used at sub-anesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced.

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate)is indicated:

as an analgesic adjunct in the maintenance of balanced general anesthesia.

as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg).

The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses

Vital signs should be monitored routinely.

Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY).

The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent.

High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area

Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced.

Head Injuries. SUFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compro-mised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits

There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%).

Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apne A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depresse respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assiste or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supporti measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

See dosage range chart for the use of SUFENTA by intravenous injection 1) in doses of up to 8 µg/kg as an analgesic adjunct to general anesthesia, and 2) in doses ≥8 µg/kg as a primary anesthetic agent for induction and maintenance of anesthesia with 100% oxygen.

Usage in Children: For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 µg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of up to 25-50 µg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.

Premedication: The selection of preanesthetic medications should be based upon the needs of the individual patient.

Neuromuscular Blocking Agents: The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

ADULT DOSAGE RANGE CHART

TOTAL DOSAGE	MAINTENANCE DOSAGE
ADMINISTRATION WITH NITROUS OXIDE/OXYGEN FOR SURGICAL PROCEDURES LASTING UP TO EIGHT HOURS:	
• TOTAL DOSAGE REQUIREMENTS OF 1µG/KG/HR OR LESS ARE RECOMMENDED	
1-2 µg/kg: Expected duration of anesthesia 1-2 hours. Approximately 75% or more of total SUFENTA dosage may be administered prior to intubation. Administered with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.	**10-25 µg (0.2-0.5 ml):** as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to remaining operative time anticipated.
2-8 µg/kg: Expected duration of anesthesia 2-8 hours. Approximately 50 to 75% of total SUFENTA dosage may be administered prior to intubation. Administered with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures. At dosages in this range, SUFENTA has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli, provide hemodynamic stability, and provide relatively rapid recovery.	**10-50 µg (0.2-1 ml):** as determined by changes in vital signs that indicate stress or lightening of analgesia. Supplemental dosages should be individualized, and adjusted to the remaining operative time anticipated.
ADMINISTRATION WITH 100% OXYGEN	
8-30 µg/kg: (anesthetic doses) administered with 100% oxygen and a muscle relaxant. SUFENTA has been found to produce sleep at dosages ≥8 µg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. At dosages in this range of up to 25 µg/kg, catecholamine release is attenuated. Dosages of 25-30 µg/kg have been shown to block sympathetic responses including catecholamine release. High doses are indicated in patients undergoing major surgical procedures, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance. Postoperative mechanical ventilation and observation are essential at these dosages due to extended postoperative respiratory depression.	**25-50 µg/kg (0.5-1 ml):** as determined by changes in vital signs that indicate stress and lightening of anesthesia.

In patients administered high (anesthetic) doses of SUFENTA, it is essential that qualified personnel and ade facilities are available for the management of postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

For purposes of administering small volumes of SUFENTA accurately, the use of a tuberculin syringe or equiv is recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to admi whenever solution and container permit.

HOW SUPPLIED: SUFENTA (sufentanil citrate) Injection for intravenous use is available as:

NDC 50458-050-01	50 µg/ml, 1 ml ampoules in packages of 10	
NDC 50458-050-02	50 µg/ml, 2 ml ampoules in packages of 10	Protec
NDC 50458-050-05	50 µg/ml, 5 ml ampoules in packages of 10	Store at room

JANSSEN
PHARMACEUTICA

Janssen Pharmaceutica Inc.
Piscataway, NJ 08854

U.S Patent No. 3
78
May 1984, Janu

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Olympus LF-1

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The Olympus LF-1 Intubation Scope designed specifically for:

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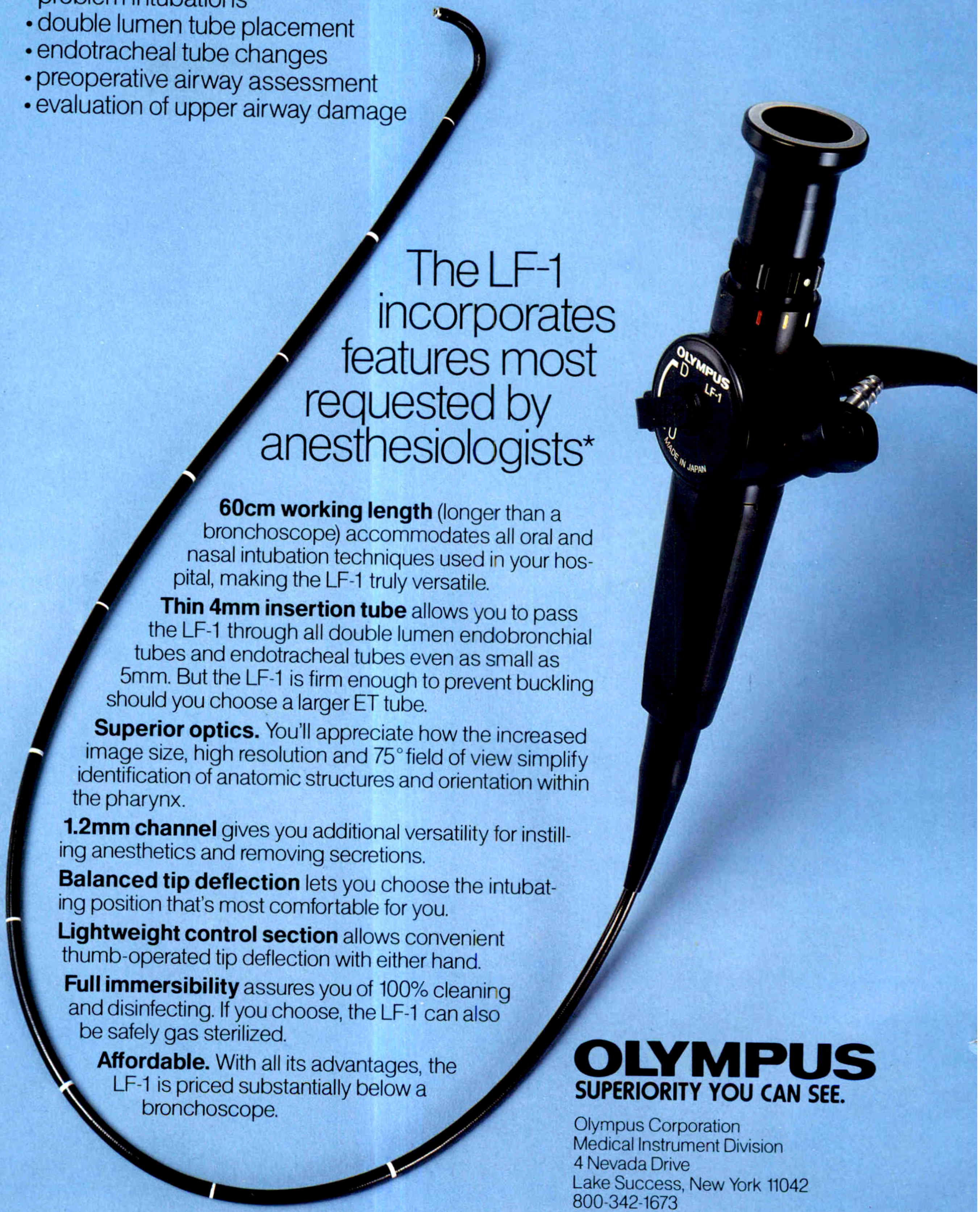

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Sponsors an annual scientific meeting (Congress) which is held in March each year

Funds anesthesia-related research through the IARS B.B. Sankey Anesthesia Advancement Award

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Annual Dues for Members and Associate Members: $50.00 U.S.; $61.00 foreign. These memberships are entered on a calendar year basis only.

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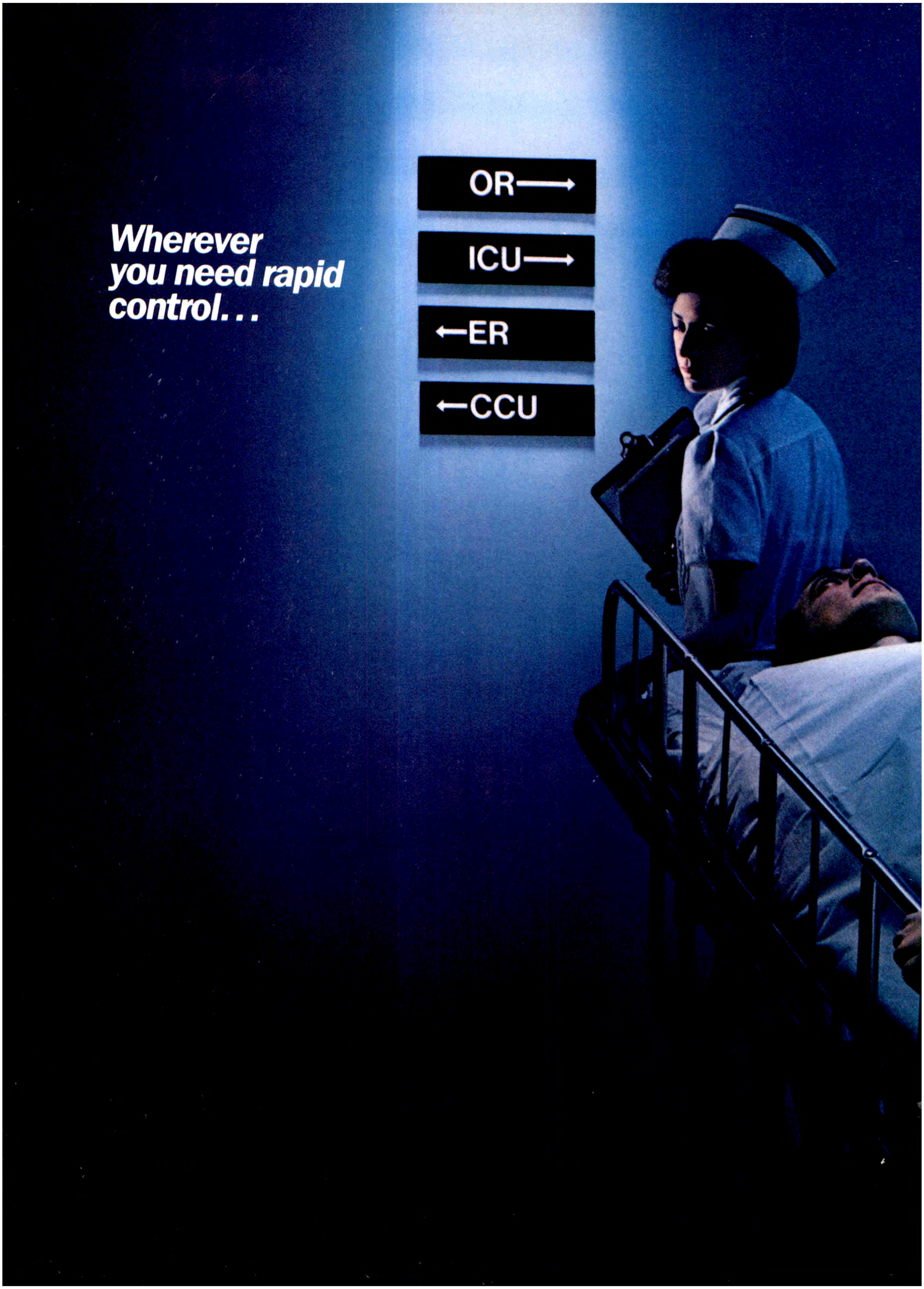
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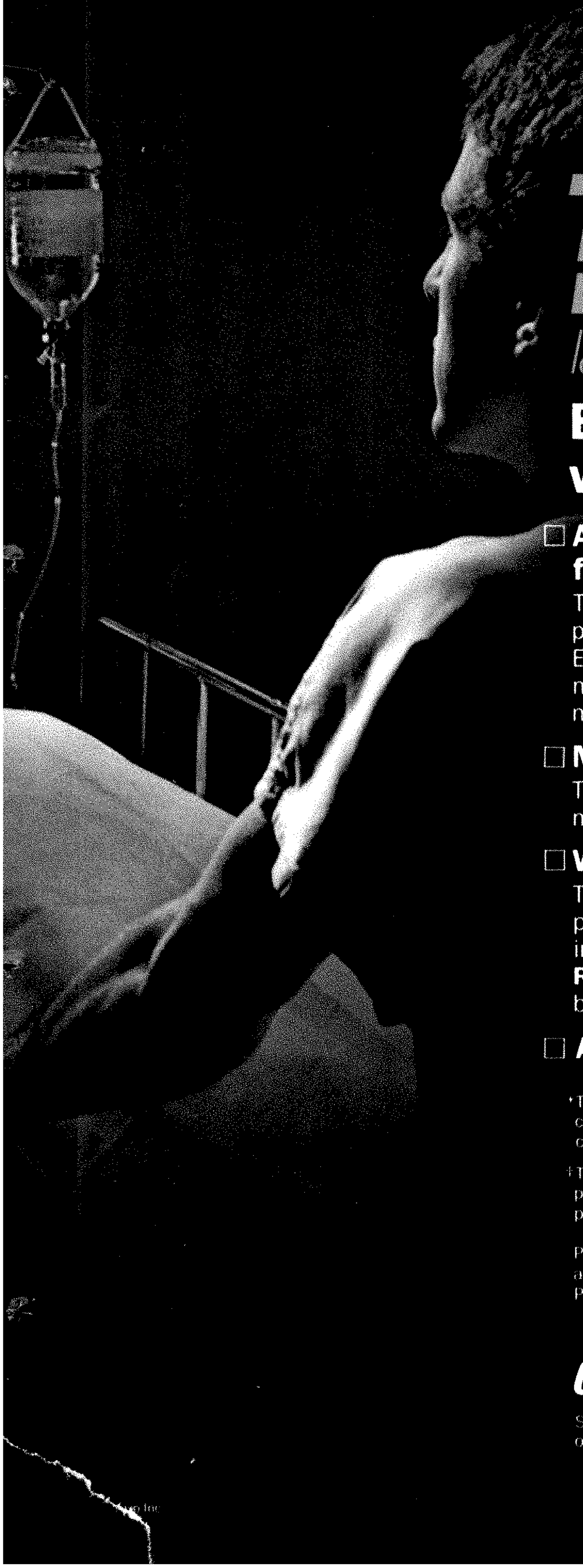

TRANDATE™
INJECTION
labetalol HCl/Glaxo 20 ml, 5 mg/ml

Blood pressure control when you want it. . . *fast*

☐ **Acts in one minute; full effect in five to ten minutes**

TRANDATE Injection reduces blood pressure and peripheral resistance smoothly and predictably. Each IV dose achieves its full effect in five to ten minutes. After control is attained, blood pressure may be controlled for up to 12 to 16 hours.

☐ **Maintains heart rate and cardiac output**

TRANDATE Injection has no significant effect on myocardial function.*

☐ **Well tolerated**

The most common adverse reactions include postural hypotension,† dizziness,† paresthesias, increased sweating and nausea. See **ADVERSE REACTIONS** section of Prescribing Information before administering.

☐ **An original product of Glaxo research**

*TRANDATE Injection is contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock and severe bradycardia.

†The episodes of postural hypotension and dizziness occurred primarily in one study in which patients were placed in an upright position within three hours of dosing for evaluation.

Patients should be kept in the supine position during IV drug administration. See **DOSAGE AND ADMINISTRATION** section of Prescribing Information before initiating therapy.

Glaxo

See next page for a Brief Summary of Prescribing Information.

o Inc

TRN200

March 1986

TRANDATE® Injection

labetalol HCl/Glaxo 20 ml, 5 mg/ml

RAPID, PREDICTABLE BLOOD PRESSURE CONTROL

TRANDATE®
(labetalol hydrochloride)
Injection

BRIEF SUMMARY
OF PRODUCT INFORMATION

INDICATIONS AND USAGE: TRANDATE® (labetalol HCl) Injection is indicated for control of blood pressure in severe hypertension.

CONTRAINDICATIONS: TRANDATE® Injection is contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).

WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.

In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).

Ischemic Heart Disease: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, following abrupt cessation of therapy with some beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TRANDATE is planned, the patient should be carefully observed and should be advised to limit physical activity. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken.

Nonallergic Bronchospasm (eg, chronic bronchitis and emphysema): Since TRANDATE Injection at the usual intravenous therapeutic doses has not been studied in patients with nonallergic bronchospastic disease, it should not be used in such patients.

Pheochromocytoma: Intravenous labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma; higher than usual doses may be required. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.

Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions** under **PRECAUTIONS**).

Rapid Decreases of Blood Pressure: Caution must be observed when reducing severely elevated blood pressure. Although such findings have not been reported with intravenous labetalol HCl, a number of adverse reactions, including cerebral infarction, optic nerve infarction, angina and ischemic changes in the electrocardiogram, have been reported with other agents when severely elevated blood pressure was reduced over time courses of several hours to as long as 1 or 2 days. The desired blood pressure lowering should therefore be achieved over as long a period of time as is compatible with the patient's status.

PRECAUTIONS: General: ***Impaired hepatic function*** may diminish metabolism of TRANDATE® Injection.

Hypotension: Symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving TRANDATE Injection. Therefore, the patient's ability to tolerate an upright position should be established before permitting any ambulation.

Jaundice or Hepatic Dysfunction: On rare occasions, oral labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.

Information for Patients: The following information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. During and immediately following (for up to 3 hours) TRANDATE Injection, the patient should remain supine. Subsequently, the patient should be advised on how to proceed gradually to become ambulatory, and should be observed at the time of first ambulation.

When the patient is started on TRANDATE Tablets, following adequate control of blood pressure with TRANDATE Injection, appropriate directions for titration of dosage should be provided (see **DOSAGE AND ADMINISTRATION**).

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted: While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see **ADVERSE REACTIONS**).

Laboratory Tests: Routine laboratory tests are ordinarily not required before or after intravenous labetalol HCl. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.

Drug Interactions: Since TRANDATE (labetalol HCl) Injection may be administered to patients already being treated with other medications, including other antihypertensive agents, careful monitoring of these patients is necessary to detect and treat promptly any undesired effect from concomitant administration.

In one survey, 2.3% of patients taking labetalol HCl orally in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl administered orally. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

TRANDATE® (labetalol hydrochloride) Injection

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol HCl in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing micro-organisms according to modified Ames tests, showed no evidence of mutagenesis.

Pregnancy Category C: Teratogenic studies have been performed with labetalol HCl in rats and rabbits at oral doses up to approximately 6 and 4 times the MRHD, respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.

Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.

Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE (labetalol HCl) Injection is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: TRANDATE® Injection is usually well tolerated. Most adverse effects have been mild and transient and, in controlled trials involving 92 patients, did not require labetalol HCl withdrawal. Symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving TRANDATE Injection. Moderate hypotension occurred in 1 of 100 patients while supine. Increased sweating was noted in 4 of 100 patients, and flushing occurred in 1 of 100 patients.

The following also were reported with TRANDATE Injection with the incidence per 100 patients as noted:

Cardiovascular System: Ventricular arrhythmia in 1.

Central and Peripheral Nervous Systems: Dizziness in 9; tingling of the scalp/skin in 7; hypoesthesia (numbness) and vertigo in 1 each.

Gastrointestinal System: Nausea in 13; vomiting in 4; dyspepsia and taste distortion in 1 each.

Metabolic Disorders: Transient increases in blood urea nitrogen and serum creatinine levels occurred in 8 of 100 patients; these were associated with drops in blood pressure, generally in patients with prior renal insufficiency.

Psychiatric Disorders: Somnolence/yawning in 3.

Respiratory System: Wheezing in 1.

Skin: Pruritus in 1.

The incidence of adverse reactions depends upon the dose of labetalol HCl. The largest experience is with oral labetalol HCl (see TRANDATE Tablet Product Information for details). Certain of the side effects increased with increasing oral dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are probably or possibly dose-related.

Labetalol HCl Daily Dose (mg)	**200**	**300**	**400**	**600**	**800**	**900**	**1200**	**1600**	**2400**
Number of Patients	522	181	606	608	503	117	411	242	175
Dizziness (%)	2	3	3	3	5	1	9	13	16
Fatigue	2	1	4	4	5	3	7	6	10
Nausea	<1	0	1	2	4	0	7	11	19
Vomiting	0	0	<1	<1	<1	0	1	2	3
Dyspepsia	1	0	2	1	1	0	2	2	4
Paresthesias	2	0	2	2	1	1	2	5	5
Nasal Stuffiness	1	1	2	2	2	2	4	5	6
Ejaculation Failure	0	2	1	2	3	0	4	3	5
Impotence	1	1	1	1	2	4	3	4	3
Edema	1	0	1	1	1	0	1	2	2

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl during investigational use and extensive foreign marketing experience.

Clinical Laboratory Tests: Among patients dosed with TRANDATE Tablets, there have been reversible increases of serum transaminases in 4% of patients tested and, more rarely, reversible increases in blood urea.

OVERDOSAGE: Overdosage with TRANDATE® Injection causes excessive hypotension which is posture sensitive and, sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain. The following additional measures should be employed if necessary: **Excessive bradycardia**—administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. **Cardiac failure**—administer a digitalis glycoside and diuretic. **Hypotension**—administer vasopressors, eg, norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. **Bronchospasm**—administer a beta$_2$-stimulating agent and/or a theophylline preparation.

If overdosage with labetalol HCl follows oral ingestion, gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral LD_{50} value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 g/kg. The intravenous LD_{50} in these species is 50 to 60 mg/kg.

DOSAGE AND ADMINISTRATION: Initiation of Dosing with TRANDATE Tablets: Subsequent oral dosing with TRANDATE Tablets should begin when it has been established that the supine diastolic blood pressure has begun to rise. The recommended initial dose is 200 mg, followed in 6-12 hours by an additional dose of 200 mg or 400 mg, depending on the blood pressure response. Thereafter, **inpatient titration with TRANDATE Tablets** may proceed as follows:

Inpatient Titration Instructions

Regimen	Daily Dose*
200 mg bid	400 mg
400 mg bid	800 mg
800 mg bid	1600 mg
1200 mg bid	2400 mg

*If needed, the total daily dose may be given in three divided doses.

While in the hospital, the dosage of TRANDATE (labetalol HCl) Tablets may be increased at one-day intervals to achieve the desired blood pressure reduction.

HOW SUPPLIED: TRANDATE® Injection, 5 mg/ml, is supplied in 20 ml (100 mg) ampuls, box of 1 (NDC 0173-0350-59).

Store between 2° and 30°C (36° and 86°F). Do not freeze.

Glaxo

Manufactured for Glaxo Inc.
Research Triangle Park, NC 27709
by Schering Pharmaceutical Corporation (PR)
Manati, PR 00701

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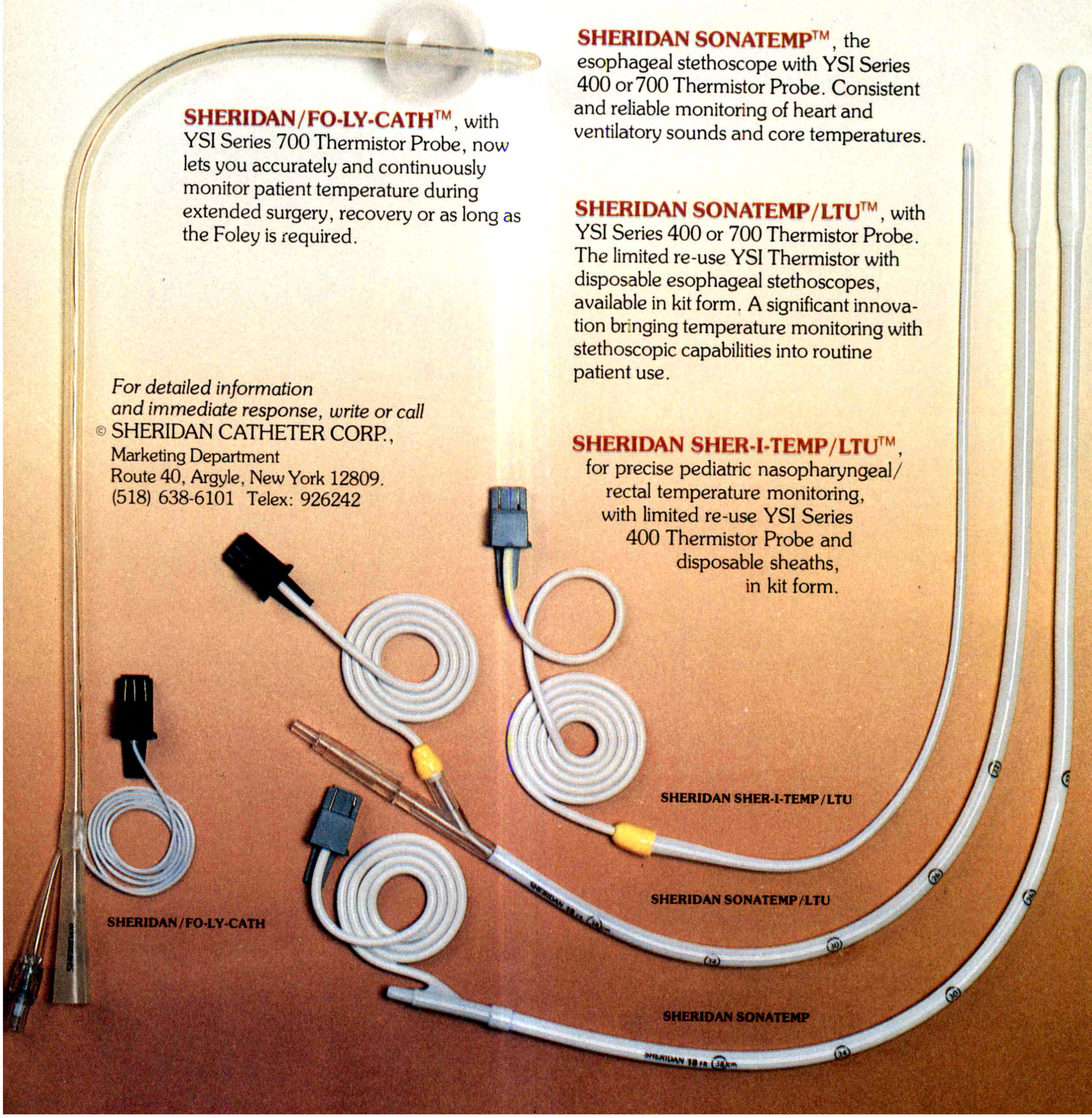

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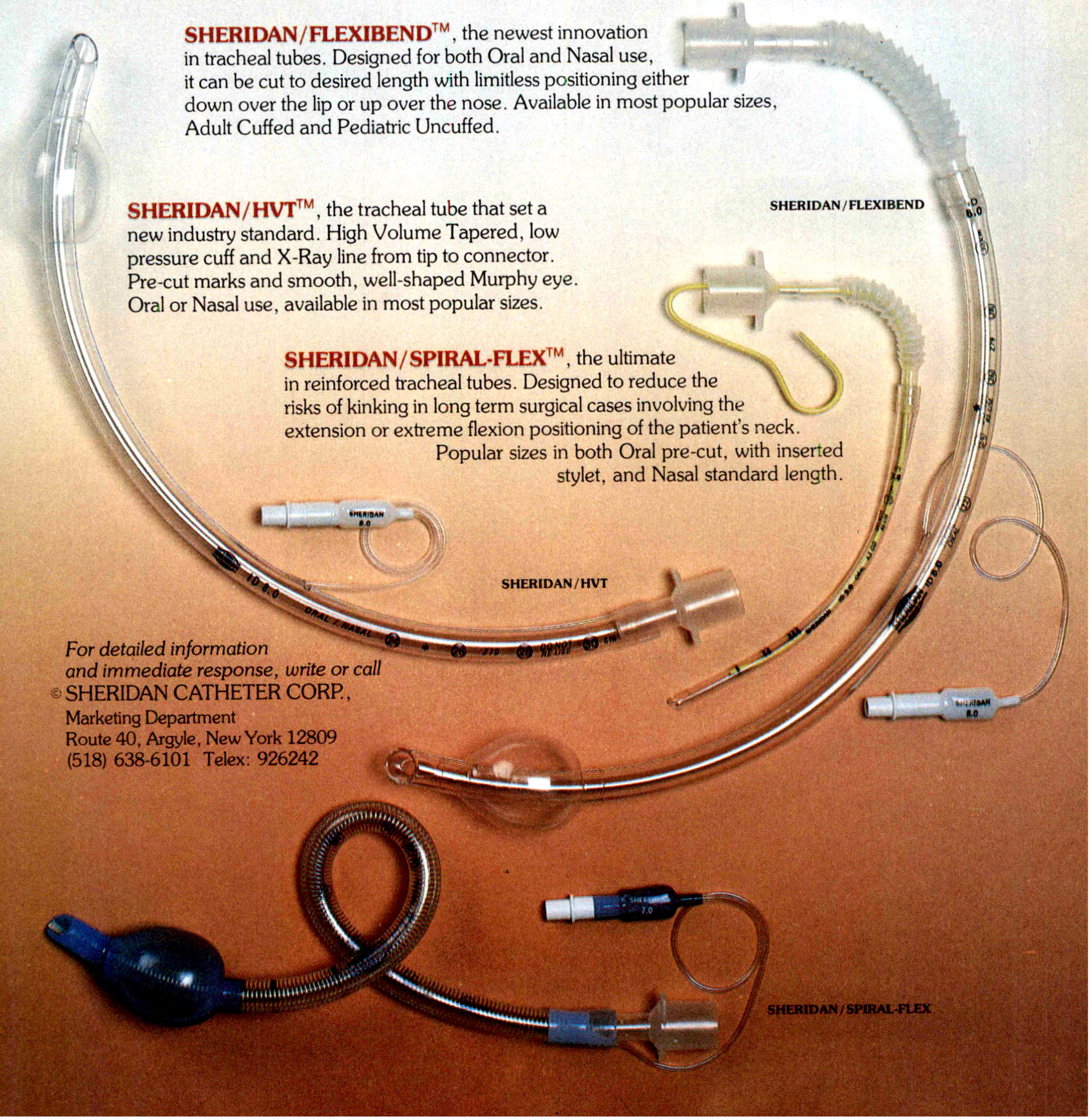

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DEVELOPMENTAL BRAIN RESEARCH

A Section of Brain Research
devoted to the publication of developmental studies

Editor-in-Chief
D. P. PURPURA, Brain Research, Office of the Dean, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, U.S.A.

Aims and Scope

Developmental Brain Research is a special section of *Brain Research* which provides a medium for prompt publication of in vitro and in vivo developmental studies concerned with the mechanism of neurogenesis, neuron migration, cell death, neuronal differentiation, synaptogenesis, myelination, the establishment of neuron-glia relations and the development of various brain-barrier mechanisms.

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(vecuronium bromide) injection

for safety and
predictability in a
wide variety of
surgical procedures.

NORCURON®

(vecuronium bromide) injection

FOR CARDIOVASCULAR STABILITY

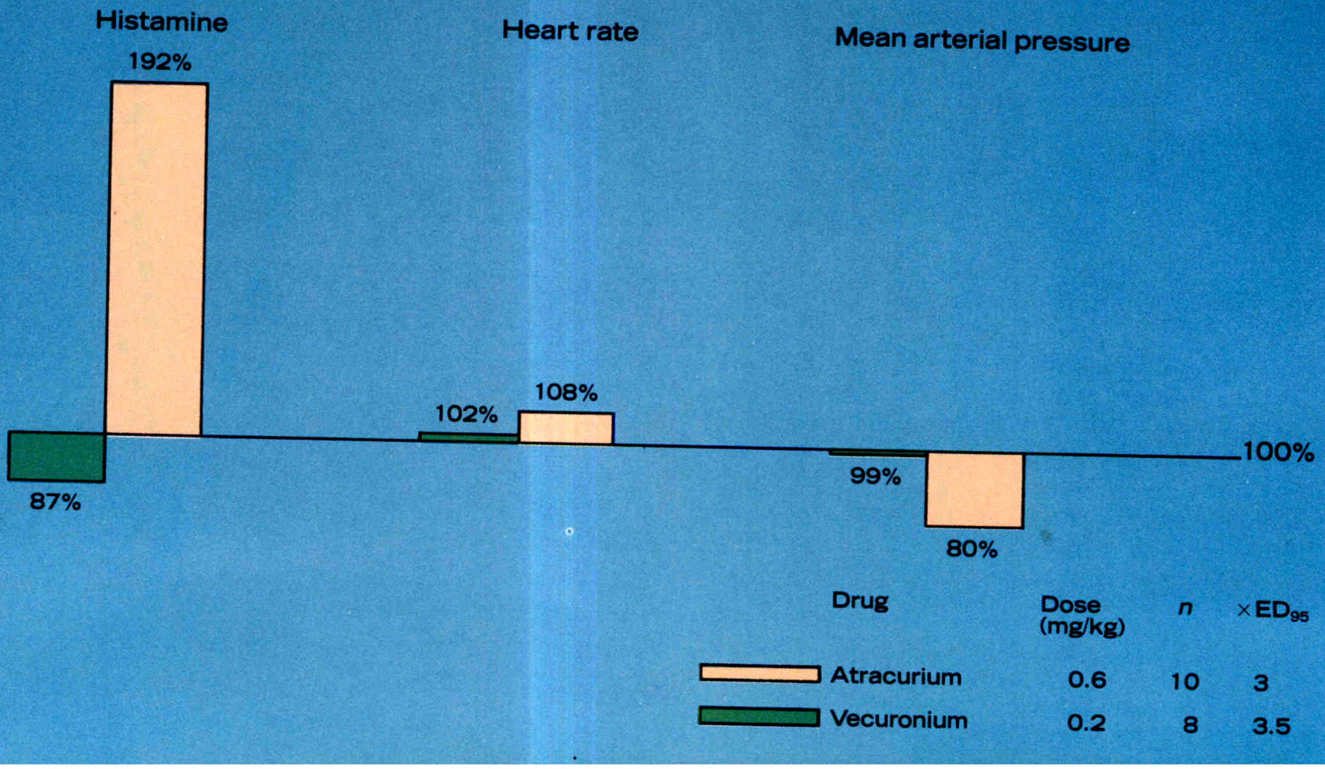
Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters.

☐ does not produce clinically significant vagolytic or cardiodepressive effects[1,2,3]

☐ indicated for cardiac surgery: coronary artery bypass grafting[1,4]

☐ indicated for patients with underlying cardiovascular problems undergoing various surgical procedures

Histamine release unlikely to occur[5]



For predictability

- ☐ may be used alone for intubation within 2½ to 3 minutes
- ☐ lacks clinically important cumulative effects

Indicated for:

- ☐ procedures lasting 25 minutes or longer
- ☐ the patient with asthma
- ☐ outpatient surgery
- ☐ pediatrics (infants seven weeks or older)

Before you decide, consider:

NORCURON® (vecuronium bromide) injection	
Histamine release	unlikely to occur
Cardiovascular effects	none clinically significant
Refrigeration	not required; stable at room temperature
Potency	reliably activated upon demand
Metabolites	3-deacetyl vecuronium
Usage in infancy	yes: seven weeks or older

NORCURON®

IN A CLASS BY ITSELF

References 1. Morris RB, Cahalan MK, Miller RD, et al: The cardiovascular effects of vecuronium (ORG NC45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 58:438-440, 1983. 2. Krieg N, Crul JF, Booij LH: Relative potency of ORG NC45, pancuronium, alcuronium and tubocurarine in anaesthetized man. *Br J Anaesth* 52:783-788, 1980. 3. Lienhart A, Guggiari M, Maneglia R, et al: Cardiovascular effects of vecuronium in man, in Agoston S et al (eds): *Clinical Experiences with Norcuron® (Org NC 45, Vecuronium Bromide)* (Symposium Geneva, 21-22 April, 1983). Current Clinical Practice Series 11, Amsterdam, Excerpta Medica, 1983, pp 150-155. 4. Gallo JA, Fries E, et al: Hemodynamic effects of bolus injection of vecuronium in cardiac surgical patients. *Anesthesiology* 61:A63, 1984. 5. Basta SJ, Savarese JJ, Ali HH, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 59:A273, 1983.

See next page for complete prescribing information.

NORCURON®

(vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON* (vecuronium bromide injection) is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2 ß, 3α, 5α, 16ß, 17ß)-3,17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide. The structural formula is:

Norcuron* is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron* (vecuronium bromide injection) is a nondepolarizing neuromusular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron* is about 1/3 more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron* is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron* doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED_{90} (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron* dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45–65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron* is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron* is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron* may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron* and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04–0.06 mg/kg of Norcuron* will produce complete neuromuscular block with clinical duration of action of 25–30 minutes. If succinylcholine is used prior to Norcuron*, the administration of Norcuron* should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron* has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron* has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15–25 minutes under balanced or halothane anesthesia. When recovery from Norcuron* neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron* is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron* induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04–0.10 mg/kg, 60–80% of Norcuron* is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025–0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65–75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35–40 minutes. The volume of distribution at steady state is approximately 300–400 ml/kg; systemic rate of clearance is approximately 3–4.5 ml/minute/kg. In man, urine recovery of Norcuron* varies from 3–35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25–50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron* (vecuronium bromide injection) has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron*; equipotent doses are of approximately the same duration as Norcuron* in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron* within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron*. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron* in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of Norcuron* during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

NO REFRIGERATION REQUIRED

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron* has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron* is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON* SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF XPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR OLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRA-ION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO SSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) yndrome, small doses of Norcuron* may have profound effects. In such patients, a peripheral nerve stimulator and use of a small est dose may be of value in monitoring the response to administration of muscle relaxants.

RECAUTIONS: Renal Failure: Norcuron* is well-tolerated without clinically significant prolongation of neuromuscular blocking ffect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in nephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for on-elective surgery, a lower initial dose of Norcuron* should be considered.

ltered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states esulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

lepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with e role the liver plays in Norcuron* metabolism and excretion (see Pharmacokinetics). Data currently available do not permit osage recommendations in patients with impaired liver function.

NDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCU-AR BLOCKING EFFECT WILL PRECLUDE INADVERTENT EXCESS DOSING.

evere Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or entilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron*.

alignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal ypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in sceptible animals (swine) to establish whether or not Norcuron* is capable of triggering malignant hyperthermia.

rcuron* has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by lequate anesthesia.

ug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron* ecuronium bromide injection) and its duration of action. If succinylcholine is used before Norcuron*, the administration of rcuron* should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating ent, initial doses of 0.04–0.06 mg/kg of Norcuron* may be administered to produce complete neuromuscular block with clinical ration of action of 25–30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron* before succinylcholine, in order to enuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the sa fashion as does Norcuron*; therefore these drugs and Norcuron* may manifest an additive effect when used together. There insufficient data to support concomitant use of Norcuron* and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron* enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents initial dose of Norcuron* may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromusc block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron* during surge unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurr paralysis may occur. This possibility must also be considered for Norcuron*. Norcuron* induced neuromuscular blockade been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases wh lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Dependi on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evalu carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron*. It is also not kno whether Norcuron* can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuro should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately mo sensitive to Norcuron* on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently availa does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron* was well-tolerated and produced no adverse reactions during extensive clinical trials. The mo frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacologic action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound a prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron* as with all curarifor drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or increase in intensity of blockade or duration of action of Norcuron* is noted from the use of thiobarbiturates, narcotic analgesic nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also caus respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron* overdosage. The possibility of iatrogenic overdosage can b minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron* can be expected to produce enhanced pharmacological effects. Residual neuromuscular blocka beyond the time period needed for surgery and anesthesia may occur with Norcuron* as with other neuromuscular blockers. Th may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral ner stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscul blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured Regonol* (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate wi usually antagonize the skeletal muscle relaxant action of Norcuron*. Satisfactory reversal can be judged by adequacy of skelet muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monito restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence o extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron* (vecuronium bromide injection) is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron* by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron* and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron* is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25–30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45–65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron* is enhanced. If Norcuron* is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron* dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron*. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron* to 0.04–0.06 mg/kg with inhalation anesthesia and 0.05–0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron* are recommended; after the initial Norcuron* injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron* lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron* on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

COMPATIBILITY: Norcuron* is compatible in solution with:

0.9% NaCl solution
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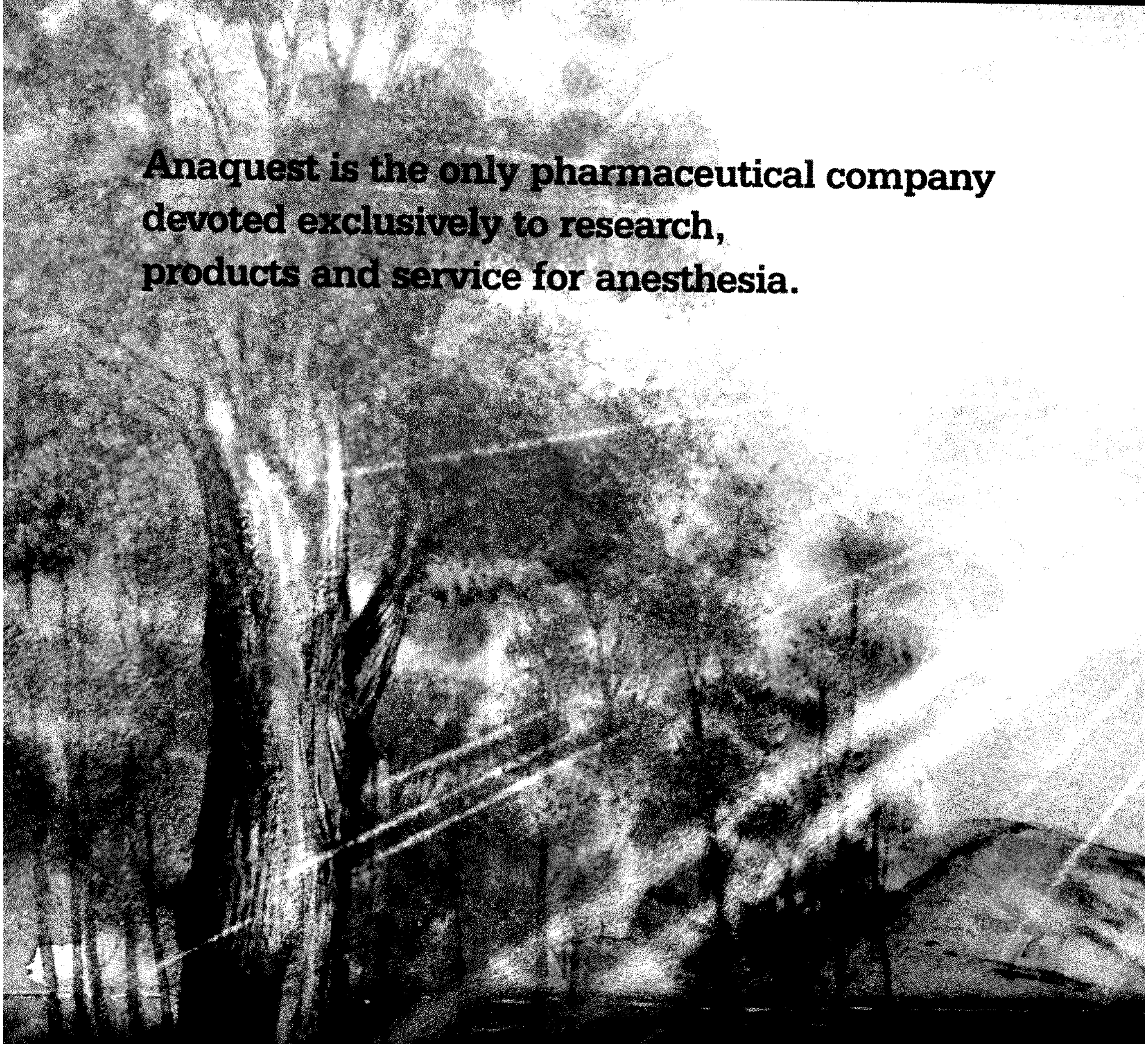

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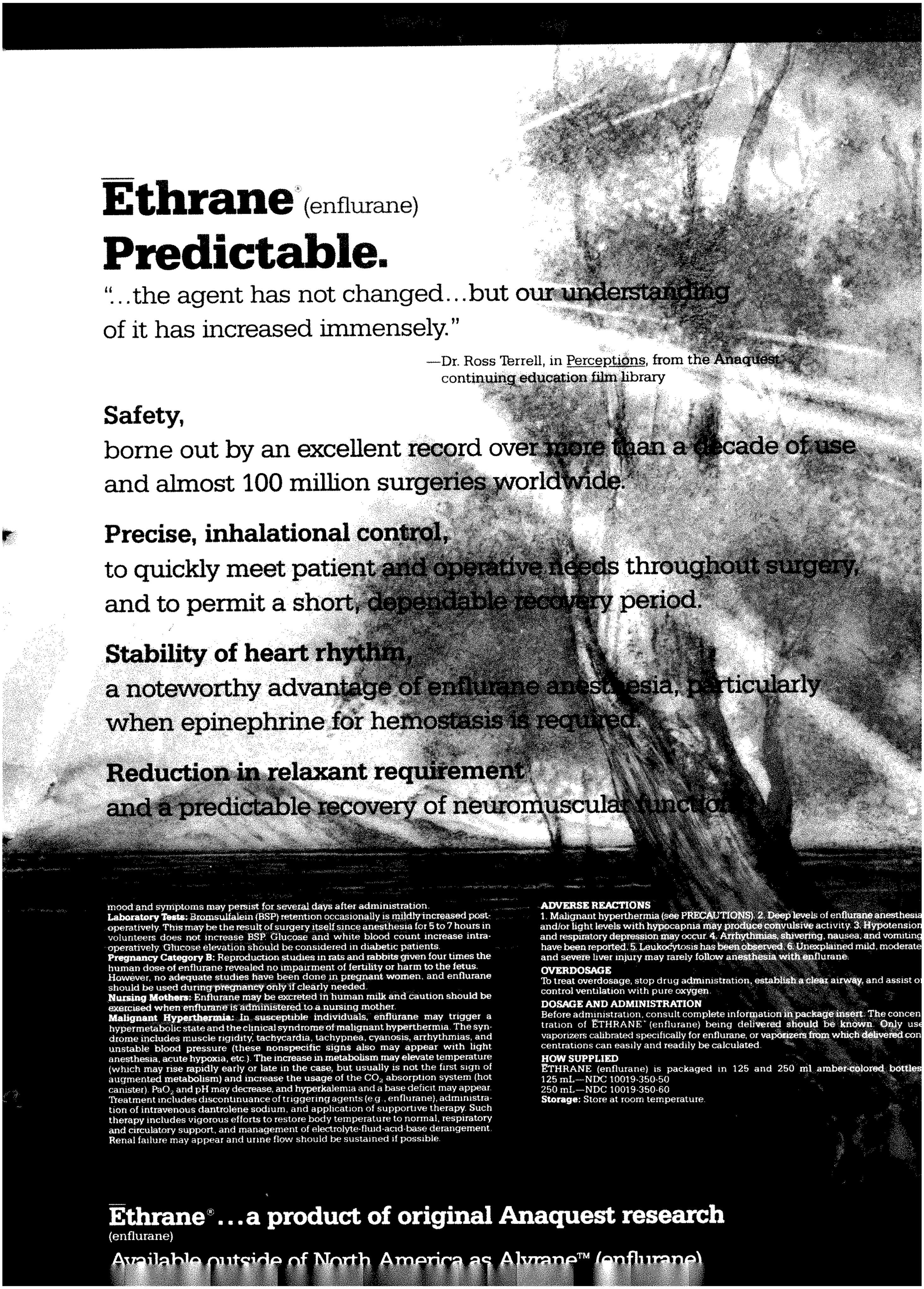

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ANESTH ANALG
1986;65:325–9

Mechanism of Differential Epidural Block

B. Raymond Fink, MD, FFARCS

FINK BR. Mechanism of differential epidural block. Anesth Analg 1986;65:325–9.

Pain block in obstetric epidural anesthesia is usually accompanied by relatively persistent retention of motor power; however, the reason for this is not entirely clear. The differential effect has been ascribed to a relatively high resistance of large fibers to conduction block. However, recent results from individual axons are incompatible with that explanation and have prompted the suggestion that greater vascularity in ventral than in dorsal roots might account for the phenomenon. To test this hypothesis, transverse sections of five sets of human dorsal and ventral C-8, T-7, and L-5 roots were examined by an immunohistochemical method that is specific for factor VIII and stains the vascular endothelium. A naive tally of the stained vessels failed to reveal any excess vascularity of the ventral roots, and the hypothesis was therefore rejected. However, it was noted at autopsy that the thin dural sleeve surrounding the roots, where epidural anesthetic is most likely to penetrate to the nerve fibers, may measure less than 5 mm from the dural sac to the intervertebral foramen, a distance probably too short to contain three internodes of motor fibers, the minimum length of fiber necessary for block by local anesthetic. This anatomy might help explain the clinical differential.

Key Words: ANATOMY—spinal nerve root, vascularity. ANESTHETIC TECHNIQUES, EPIDURAL—vascularity of nerve roots.

The epidural administration of a weak solution of local anesthetic obtunds the pain of parturition but leaves motor power more or less intact. The differential effect is quite persistent, resembling in this the differential that accompanies subarachnoid spinal block, but its mechanism is not entirely clear. Whereas spinal anesthesia presents a sympathetic efferent block that extends several segments higher than the somatic block, the epidural differential extends through, but is limited to the anesthetized segments.

The explanations devised usually invoke fiber size (1,2), the claim being that small fibers are blocked by a lower anesthetic concentration, and much more quickly, than large fibers (2). However, such claims rest on dubious extrapolations from compound action potentials (3) and are inconsistent with observations on single fibers (4,5). Single myelinated axons become blocked when the anesthetic reaches a critical concentration at two or three consecutive nodes of Ranvier (6), involving three or four internodes. Because internodal length is proportional to axonal diameter, the diffusional build-up can take somewhat longer for large fibers than for small fibers (7,5), but only by a few minutes (5). Persistent or "absolute" differences in blocking concentration were found to depend, not on axonal size as such (7), but on absence or presence of nodes of Ranvier (nonmyelination or myelination), or the presence of a heminode (junction of a nonmyelinated stretch of axon), the respective mean critical blocking concentrations being approximately in the ratios 3:2:1, or about 0.6, 0.4, and 0.2 mmol/L (roughly 15, 10, and 5 mg/dl), respectively (4). Such small differences are unlikely to account for persistent differential blocks.

In searching for other possible mechanisms of persistent differential block, one could appeal, in the case of spinal anesthesia, to frequency-dependent block (8). In this phenomenon, repetitive impulses effect a cumulative depression of sodium currents such that block occurs in the presence of a concentration of anesthetic otherwise not quite sufficient to block conduction. Preganglionic sympathetic fibers convey "tonic" repetitive vasoconstrictor impulses (9) that could, at least in theory, effect such a frequency-dependent (use-dependent) block craniad to the analgesic segments. However, such an explanation is not applicable to the differential block of epidural anesthesia. Here another factor would have to intervene, such as a greater blood flow through ventral than through dorsal spinal roots. A more rapid removal of drug from the ventral roots might selectively prevent

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Address correspondence to Dr. Fink, Department of Anesthesiology RN-10, University of Washington School of Medicine, Seattle, WA 98195.

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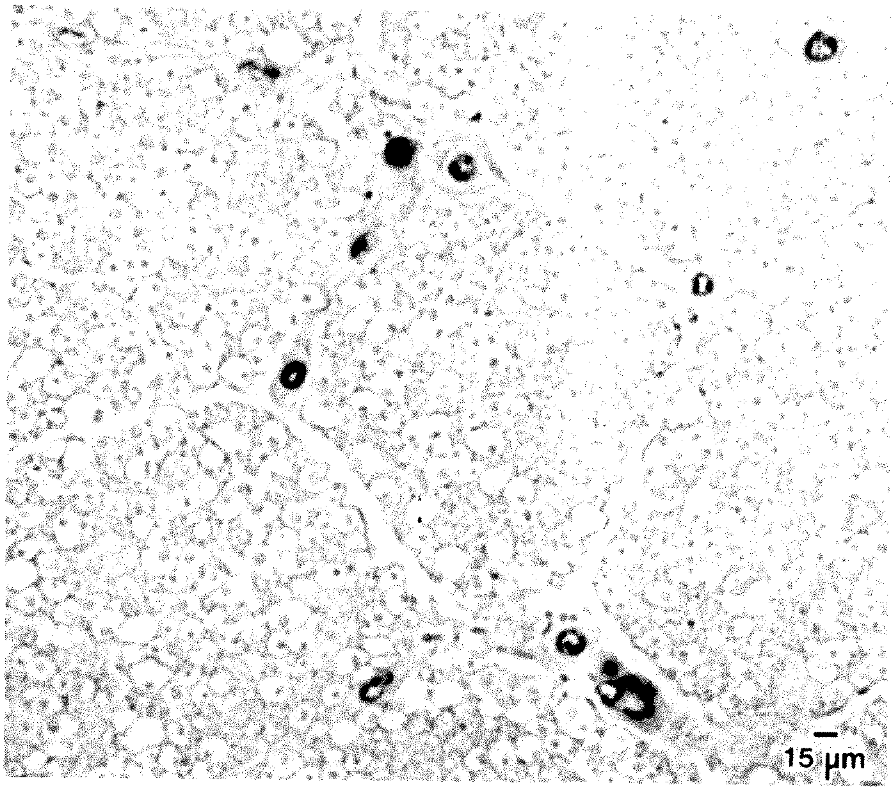

Figure 1. Transverse section of dorsal root of L-5 spinal nerve. Immunoperoxidase stain, using factor VIII antibody and avidin–biotin–horseradish peroxidase complex, which stains vascular endothelium black (magnification, × 200).

block of the skeletal motor fibers. To investigate this possibility, a morphometric study of the vascularity of the roots of human spinal nerves was performed.

Methods

Tissues were taken at autopsy from five adults who had died from causes unrelated to central nervous system disease. The roots were accessed ventrally, after removing the viscera and sawing through the pedicles of the vertebrae. The lumbar and thoracic vertebral bodies and discs were removed en bloc, thereby exposing the contents of the spinal canal with a minimum of disturbance. The ventral surface of the dural sac was slit longitudinally to expose the cauda equina and spinal cord. Intrathecal portions of the dorsal and ventral roots of C-8, T-7, and L-5 were excised and studied from each individual.

The specimens were fixed in formalin, embedded in paraffin, and cut into 5-μm transverse sections that were mounted on slides and treated by an immunohistochemical method to yield a black reaction product in the endothelium of the blood vessels (10). The immunoperoxidase technique (11) as described by Hsu et al. (12) was followed. In brief, the section undergoes preliminary digestion with pronase, and is then incubated, first, with the primary antibody contained in serum from rabbits immunized to human factor VIII; second, with serum containing the secondary antibody coupled to biotin, from goats immunized against the rabbit serum; third, with avidin–biotin–horseradish peroxidase complex, which becomes bound to the biotin in the secondary antibody; and finally, with diaminobenzidine, which yields a black reaction product at the site of the horseradish peroxidase enzyme. Sections of normal tonsillar tissue were processed concurrently to serve as a reaction control; the fibrous stroma of this tissue has a characteristic distribution of blood vessels.

Coded, enlarged prints (× 8) were prepared from black and white 35 mm microphotographs (× 25) of the entire root cross-section (Fig. 1), calibrated with the photograph of a similarly magnified micrometric scale. The vessels usually contained one or more intraluminal erythrocytes. Elsewhere erythrocytes were absent.

The cross-sectional area of the root was measured with a transparent millimetric overlay. Each endoneurial vessel was numbered in ink and the minor diameter of the lumen measured to the nearest 1 mm (equivalent to 5 μm of tissue). The sections were then counterstained with eosin and each vessel identified and examined under high power (× 400) to determine the presence or absence of a pink annulus of smooth muscle. Vessels with an annulus were excluded from the tabulation. Vessels lacking an annulus were con-

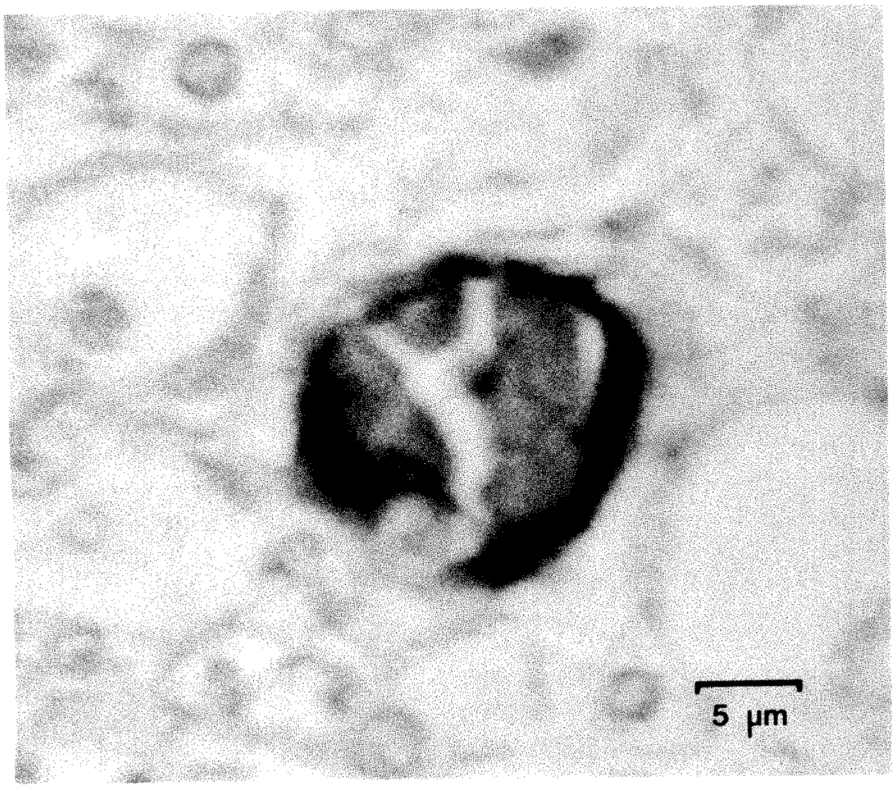

Figure 2. Micrograph of transverse section of L-5 dorsal root. Factor VIII immunoperoxidase reaction, counterstained with eosin × 2250. Note black reaction product in endothelium. The vessel diameter is about 20 μm, but the absence of a surrounding annulus of grey-stained smooth muscle indicates that this vessel is a true capillary.

sidered to be capillaries. The measurements were counted and grouped according to the minor diameter of the lumen (0, 1, 2, 3, 4, 5, and >5 mm). Tangentially-cut vessels were assigned to the 0-mm group. To enable comparisons of the total vascularities of different roots the number of vessels in each group was multiplied by πd (where d = minor diameter of the vessel), and normalized by expressing the product as capillary circumference per square mm of nerve root cross section. Statistical evaluations were performed on the summed normalized values as follows: summed values of all dorsal roots vs summed values of all ventral roots, by Student's t-test; summed segmental dorsal root values vs summed segmental ventral root values at each segmental level, by one-way ANOVA; summed within-segment group values, by Wilcoxon rank test. $P > 0.05$ was considered not significant. All observations and calculations were completed before the code was broken.

Electron micrographs were prepared from two of the roots to verify whether large vessels diagnosed as capillaries truly lacked a circumferential annulus of smooth muscle. These specimens were fixed in Karnovsky's half-strength glutaraldehyde, postfixed in osmium tetroxide, and embedded in epon; sections were stained with lead citrate and uranium acetate.

At four autopsies (two of the above and two others), the dural sleeve or "cuff" entering the intervertebral foramen had fortuitously remained intact at one or two segmental levels during the exposure. The length of the sleeve from the dural sac to the proximal border of the intervertebral foramen was measured with a millimeter rule and photographed.

Table 1. Total Circumference of Capillaries in Cross Sections of Dorsal and Ventral Roots of Spinal Nerves (μm/mm^2, mean ± SD, n = 5)

	C-8	T-7	L-5
Dorsal	2330 ± 2225	1870 ± 1845	5155 ± 6520
Ventral	1880 ± 1560	2105 ± 1995	2795 ± 2615

Results

The endothelium of many endoneurial vessels, including large ones exceeding 20 μm in diameter (Fig. 2), was in direct contact with nerve fibers or connective tissue, without intervening smooth muscle. The number of capillaries in the different size groups varied widely between the roots from a given segment and between the roots from the same subject. However, when weighted for circumference and normalized per unit cross section, the values (Table 1) showed little variation. The values for dorsal vs ventral roots did not differ significantly, either when summed over

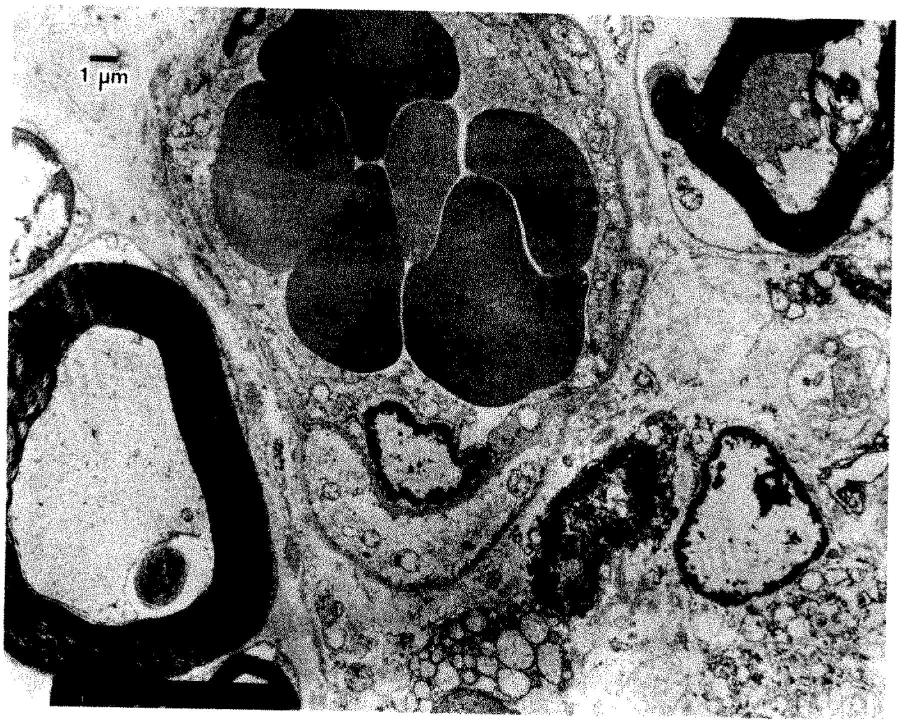

Figure 3. Electron micrograph of large capillary in L-5 dorsal root. Calibration bar, 1 µm. Note red blood cells in lumen of vessel separated from a myelinated nerve fiber by little more than the thickness of the vascular endothelium. Magnified approximately 3500 diameters.

all the segments or when compared at each cervical, thoracic, and lumbar segmental level. Summed across the different segments, the normalized values in each size group did not differ significantly in size groups 0, 1, 2, 3, and 4. The values for groups 5 and >5 were significantly smaller ($P < 0.05$). In electron micrographs, blood vessels were easily recognizable by the presence of erythrocytes in the lumen (Fig. 3). The lengths of the four dural sleeves of lumbar and lower thoracic spinal nerves medial to the intervertebral foramen measured at autopsy were 5, 6, 6, and 8 mm, respectively. The reliability of the measurements is limited because relationships may have been disturbed by the method of sampling.

Discussion

The result of the vascularity study was essentially negative. No excess vascularity was present in the ventral roots, either collectively or in individual spinal segments. The hypothesis that differential vascularity in dorsal and ventral roots may contribute to differential epidural block was therefore rejected.

The examined roots presented relatively few vessels in group 1, the size typical of capillaries in several other tissues (13,14). About 50% of the capillaries had a minor diameter exceeding 5 µm, in some cases exceeding 20 µm (Table 1). The abundance of large capillaries presumably minimizes resistance to blood flow in the nutrient vessels of the roots.

Previous measurements of dural sleeve lengths have not been found; the present ones are consistent with the calibrated photograph in Bassett's Stereoscopic Atlas (15). Opinion varies on the precise site of epidural block (1,16); it is generally held that because the dura of the sleeve is thinner than elsewhere, anesthetic deposited extradurally probably first reaches a blocking concentration in the roots within the sleeve. However pharmacokinetic data on this point are not available. The measured lengths of sleeve are less than three times the length of a large fiber internode (17), and if this is a principal site of epidural block, may constitute a basis for the differential sparing of motor function observed in the first hours of continuous epidural block as used in obstetric regional anesthesia.

Sources of reagents were the following: pronase, Calbiochem-Behring, PO Box 12087, San Diego, CA 92112; primary antibody, Dako Corporation, 22 N Milpas Street, Santa Barbara, CA 93103; secondary antibody and ABC complex, Vector Laboratories, Inc., 1429 Rollins Road, Burlingame, CA 94104; diaminobenzidine, Polyscience, Inc., Paul Valley Industrial Park, Warrington, PA 18979.

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Naloxone Does Not Antagonize the Analgesic Effects of Inhalation Anesthetics

Laurence L. Levin, MD, Peter M. Winter, MD, Edwin M. Nemoto, PhD,
Marc Uram, MD, PhD, and Marina R. Lin, MS

LEVIN LL, WINTER PM, NEMOTO EM, URAM M, LIN MR. Naloxone does not antagonize the analgesic effects of inhalation anesthetics. Anesth Analg 1986;65:330–2.

A previous demonstration that the ratio of analgesic to anesthetic endpoints is not constant across inhalation anesthetic agents implies that more than one mechanism of action may be operant in general anesthesia. We hypothesized that the endogenous opiate systems might account for this observed disparity in ratios. The tail flick ED_{50} ($TFED_{50}$) in response to a heat stimulus, as an index of analgesia, and MAC as an index of anesthesia, were determined in rats treated with either saline or naloxone, 20 mg/kg, and exposed to halothane, enflurane, or isoflurane. Our findings confirmed those of Deady et al., showing a lack of uniformity of ratios of $TFED_{50}$/MAC, with values of 0.90 ± 0.03 for halothane, 0.80 ± 0.04 for enflurane, and 0.70 ± 0.04 for isoflurane. Naloxone had no effect on $TFED_{50}$, MAC, or their ratio. If the endogenous opiate system were involved in the analgesic effect of general anesthetics, naloxone would have affected the ratios. We conclude that opiate systems are not involved in the analgesic action of general anesthetics.

Key Words: ANESTHETICS, VOLATILE—enflurane, halothane, isoflurane. ANTAGONISTS, NARCOTIC—naloxone. THEORIES OF ANESTHETIC ACTION—endorphins.

Controversy exists concerning the role of opiate receptors in the mechanism of action of inhalation anesthetics. Finck et al. and Berkowitz et al. have demonstrated a consistent antianesthetic effect of naloxone in several species using different experimental methods (1,2). However, other groups have failed to confirm these findings (3,4). In particular, a careful study by Harper et al. (4) showed that naloxone doses as high as 50 mg/kg failed to alter halothane MAC in the rat.

A potential solution to the disagreement may be in the definition of anesthesia. The work of Harper et al. was carried out at the usual concentrations of anesthesia relevant to MAC testing, whereas several studies of Finck et al. were done at subanesthetic, analgesic dose levels. We hypothesized that a second mechanism of action for inhalation anesthetics may exist, producing opiate-mediated analgesia at subanesthetic concentrations, and thus subject to antagonism by naloxone. This suggested mechanism may be overwhelmed and rendered undetectable by the higher concentrations used in surgical levels of anesthesia and classically measured by MAC testing methods.

Clinical experience inclines us to believe that inhalation anesthetics vary in analgesic potency at equal MAC fractions, i.e., methoxyflurane high and halothane low. It has been previously suggested that the ratio of an analgesic endpoint to an MAC endpoint for individual anesthetics should be consistent across agents if one mechanism of action is involved, but variable if a second effect such as opiate receptor-mediated analgesia is operant (5). A study by Deady et al. (5) showed that there is variability of such ratios across agents. If the mechanism of analgesia is opiate-mediated, the administration of naloxone prior to testing should equalize the ratios. If tail flick in response to a heat stimulus is used as an analgesic endpoint ($TFED_{50}$), and if naloxone antagonizes the analgesic action without appreciably affecting MAC, both $TFED_{50}$ and $TFED_{50}$/MAC should decrease after naloxone administration.

Methods

Forty-six male, Sprague Dawley rats weighing 190–210 g were studied, 18 with halothane, 12 with enflurane, and 16 with isoflurane. Rats were placed in individual

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Address correspondence to Dr. Winter, Department of Anesthesiology, University of Pittsburgh, Pittsburgh, PA 15261.

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Table 1. Anesthetic Concentration (%ATM) ± SEM

	$TFED_{50}$		MAC		$TFED_{50}$/MAC	
Anesthetic	Naloxone	Saline	Naloxone	Saline	Naloxone	Saline
Halothane ($n = 18$)	0.96 ± 0.04	0.93 ± 0.04	1.06 ± 0.04	1.04 ± 0.05	0.91 ± 0.02	0.90 ± 0.03
Enflurane ($n = 12$)	2.05 ± 0.21	2.02 ± 0.17	2.49 ± 0.14	2.49 ± 0.13	0.82 ± 0.06[a]	0.80 ± 0.04[a]
Isoflurane ($n = 16$)	0.87 ± 0.07	0.89 ± 0.06	1.31 ± 0.06	1.28 ± 0.07	0.66 ± 0.04[b]	0.70 ± 0.04[b]

Abbreviation: $TFED_{50}$, tail flick ED_{50}.
[a] $P < 0.05$, Naloxone and saline groups $TFED_{50}$/MAC for enflurane compared to halothane.
[b] $P < 0.001$, Naloxone and saline groups $TFED_{50}$/MAC for isoflurane compared to halothane.

2-L plexiglass cylinders, each with an air-flow rate of 3 L/min. Rectal temperatures were monitored and maintained with heat lamps at 37.1 ± 0.04°C (SEM) for both control and naloxone groups. A timed heart dolorimeter was used to measure tail flick latency (TFL) after the tails were blackened with india ink. The heat setting was adjusted in preliminary studies to obtain baseline TFL between 5 and 6 sec; a maximum baseline TFL of 7.5 sec was accepted. In order to prevent injury to the animals, 10 sec of heat application was taken as the cut-off for absence of tail flick response. The TFL at each point was measured in triplicate. The analgesic endpoint was defined as the anesthetic concentration producing a 2-sec increase above the baseline TFL for each rat.

Baseline TFLs were determined 30 min after the air breathing rats were placed into the test apparatus. Thereafter, the rats were equilibrated for 30 min breathing either halothane (0.45%), enflurane (0.88%) or isoflurane (0.55%)—approximately equipotent fractions of MAC.

Inspired anesthetic concentrations were measured by gas–liquid chromatography. One ml of the inspired gas was drawn into a gas-lock Hamilton syringe and injected into a Model 3700 Varian gas–liquid chromatograph with a flame ionization detector and a 6-ft glass column packed with 3.0% SE-30. The injector/column/detector temperatures were set at 120/60/120°C, with a N_2 carrier gas flow rate of 30 ml/min. The anesthetic peaks were integrated by a Shimadzu CRIA microprocessor and the anesthetic concentrations calculated from standard calibration curves. The calibration curves were prepared with known standards of the anesthetic vapor samples derived from air saturated samples. The saturated vapor pressures of the anesthetics were calculated according to the Antonine equation:

$$\text{Log P (mm Hg)} = A - \frac{B}{t + C}$$

where P is the vapor pressure; t is the temperature in °C; and A, B, and C are constants. The constants A, B, and C for the anesthetics are the following: halothane, 7.723, 1.565, and 273.15; enflurane, 7.967, 1678.4, and 273.16; and isoflurane, 8.056, 1664.58, and 273.16. The v/v percent of saturated vapor pressure was calculated by dividing the saturated vapor pressure by atmospheric pressure and multiplying by 100.

After baseline TFL measurements, the inspired anesthetic concentration was increased in increments of 20% of MAC, followed by 30 min equilibration and a 15-min test period. At each increment, TFL was tested until analgesia was produced. Thereafter, MAC testing was begun, and the inspired gas concentration progressively increased in a like manner until the anesthetic endpoint was achieved. One half of the rats in each test group received 20 mg/kg naloxone HCl (Endo Laboratories) by subcutaneous injection at 20 min and an additional 10 mg/kg 10 min prior to the first test on the anesthetic. Thereafter 10 mg/kg was injected 10 min before each test at increasing anesthetic concentrations. The other half of the rats received similar volumes of 0.9% NaCl in the same manner. The observer doing the testing did not know which solution he administered. Four days later, the entire study was repeated, but rats previously studied with naloxone were retested with saline and vice versa.

$TFED_{50}$, MAC, and $TFED_{50}$/MAC for each anesthetic with naloxone and 0.9% NaCl pretreatment were statistically evaluated by analysis of variance, and the values tested for significant differences by the Student's–Newman–Keul's test. $TFED_{50}$/MAC for each anesthetic was statistically analyzed after conversion to log values. A maximum P value of 0.05 was accepted as statistically significant.

Results

$TFED_{50}$ with enflurane in control (saline-treated) rats was 2.02 ± 0.17% ($\bar{x}$ ± SEM), and higher than with halothane (0.93 ± 0.04%) or isoflurane (0.89 ± 0.06%) (Table 1). None was affected by naloxone. Enflurane MAC was 2.49 ± 0.13% and significantly higher than MAC for isoflurane and halothane. Isoflurane MAC was also significantly higher than halothane MAC. Naloxone did not affect MAC.

$TFED_{50}$/MAC for halothane with and without naloxone was significantly higher than that for isoflurane or enflurane. The difference between the isoflurane and enflurane ratios was statistically significant. $TFED_{50}$/MAC was not affected by naloxone for any of the anesthetics.

Discussion

The lower $TFED_{50}$/MAC ratios of enflurane and isoflurane indicate that these agents are stronger analgesics than halothane at subanesthetic concentrations. The variation in ratios between agents implies that the mechanism producing analgesia may differ from that producing anesthesia. The values obtained for $TFED_{50}$/MAC in rats confirm those of Deady et al. obtained in mice (5). In contrast to Deady et al., we demonstrated some degree of analgesia with halothane, the $TFED_{50}$/MAC ratio being less than one.

In order to compare our study with previously published work, and because it is a reproducible and accepted endpoint, we used TFL as an analgesic endpoint. We believe that an alternative stimulus system that would give a clean endpoint at lower anesthetic concentrations, thereby resulting in lower $TFED_{50}$/MAC ratios, might conceivably have given more clean-cut ratio differences.

That naloxone did not alter $TFED_{50}$ or $TFED_{50}$/MAC for any of the anesthetics tested indicates that opiate receptors are not involved in either the analgesia or the anesthesia produced by these agents. The dose of naloxone we administered is far in excess of that needed to antagonize opiate receptor-mediated responses. Additionally, eight rats injected by the intraperitoneal route yielded $TFED_{50}$ and $TFED_{50}$/MAC values similar to those obtained after subcutaneous injection. We conclude that opiate receptors do not play a role in the analgesia produced by these inhalation agents at subanesthetic concentrations.

Our finding that MAC is unaltered by naloxone is in agreement with both our own previous study (4) and the studies of others. Neither naloxone nor naltrexone increased MAC in halothane-anesthetized dogs (6). MacLeod et al. demonstrated no significant alteration in halothane or halothane/nitrous oxide requirements in anesthetized humans after administration of 1.2 mg naloxone (7). In vitro, halothane does not displace specific dihydromorphine binding (8). In dogs, cerebral oxygen consumption is not increased upon administration of naloxone during halothane anesthesia, whereas it is increased when the same agent is administered to dogs under narcotic anesthesia (9).

In conclusion, our results indicate that opiate receptor systems are involved with neither anesthetic mechanisms of action nor with the mechanisms of analgesia at low concentrations of inhalation agents. Our findings confirm those of Deady et al., that $TFED_{50}$/MAC ratios vary between anesthetics, and that this may implicate the existence of more than one mechanism of action for inhalation anesthetics.

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ANESTH ANALG 1986;65:333–6

Motor Blockade During Epidural Anesthesia

Adrien Van Zundert, MD, PhD, Leo Vaes, MD, Paul Van der Aa, MD,
Agnes Van der Donck, MD, and Herman Meeuwis, MD

VAN ZUNDERT A, VAES L, VAN DER AA P, VAN DER DONCK A, MEEUWIS H. Motor blockade during epidural anesthesia. Anesth Analg 1986;65:333–6.

The effects of lumbar epidural anesthesia (LEA) on a previously described test of function of the rectus abdominalis muscle (the RAM-test) were compared with the effects of LEA on the Bromage test of muscle power in the hips and legs in 20 women having elective cesarean sections under LEA using 0.5% bupivacaine with epinephrine 1:200,000. The results showed no statistically significant correlation between the two tests. We conclude that zones of differential somatic motor blockade are present during LEA and that in obstetrics the RAM-test is the more appropriate test for evaluating the effects of LEA on somatic motor function. Use of the RAM-test is suggested in situations where one is interested in motor function of the abdominal wall muscles under LEA.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL. ANESTHESIA—obstetric.

Various tests (1–6) have been used to evaluate motor blockade during lumbar epidural anesthesia (LEA). We concluded from an earlier study (7) in 877 parturients receiving successful LEA with 0.125% bupivacaine plus epinephrine 1:800,000 for vaginal delivery that evaluation of function of the rectus abdominalis muscle (the RAM-test) is a more appropriate test in evaluating abdominal motor function than is the Bromage test, which evaluates the motor strength of the hips and legs.

To determine whether this conclusion is also valid when higher doses and stronger concentrations of local anesthetic are used, we performed both the Bromage and the RAM-test in 20 women having elective cesarean sections performed under LEA using 0.5% bupivacaine with epinephrine 1:200,000.

Methods

Lumbar epidural anesthesia with 100–125 mg (mean 115 mg) of 0.5% bupivacaine plus epinephrine 1:200,000, using the L2-3 interspace, was given to 20 randomly selected women undergoing elective cesarean section. All women were ASA physical status I, with weights ranging from 56 to 83 kg and ages ranging from 20 to 29 yr. All women had excellent anesthesia and needed no other analgesic supplementation.

In each patient the degree of motor blockade was assessed by the Bromage method (Table 1) and the RAM-test (Fig. 1). The RAM-test was performed as follows (Fig. 1): starting from the completely supine position (no pillow and legs extended) the patient was asked to come slowly and with a curled trunk to the supine position. If the power of the abdominal muscles was too weak, the woman could not come slowly to the sitting position with a curled trunk (8). Scoring the power of the rectus abdominalis muscle was done as shown in Figure 1. Power was scored as 0% when no tension of the abdominal muscles could be felt during the effort.

The degree of motor blockade in the abdominal muscles (RAM-block) associated with LEA is the dif-

Table 1. Evaluation of the Degree of Motor Blockade during Lumbar Epidural Anesthesia by Bromage's Method (1)

Bromage criteria	Degree of motor block	(%)
Free movement of legs and feet	None	(0%)
Just able to flex the knees with free movement of the feet	Partial	(33%)
Unable to flex the knees but with free movement of the feet	Almost complete	(66%)
Unable to move legs or feet	Complete	(100%)

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Address correspondence to Dr. Vaes, St-Elisabeth Hospital, Department of Anesthesiology and Reanimation, 2300 Turnhout, Belgium.

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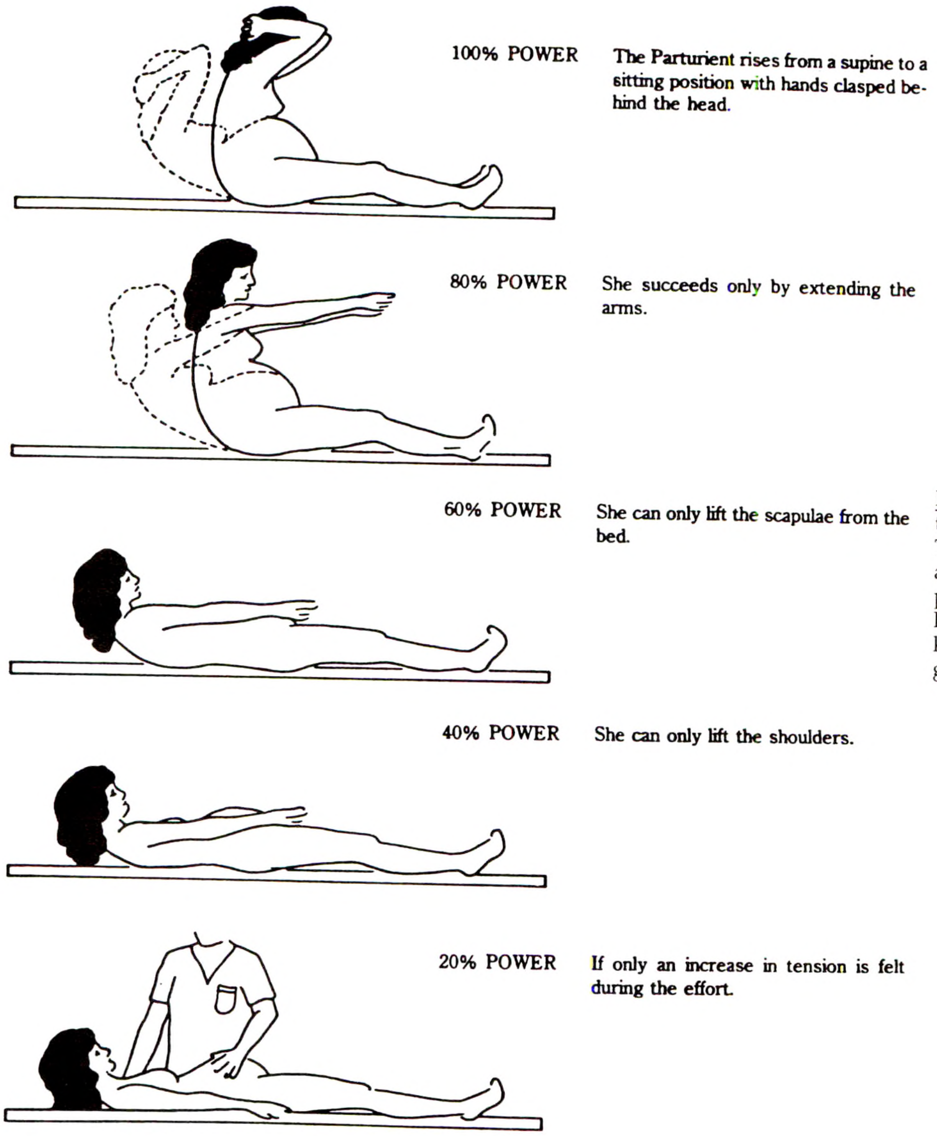

100% POWER The Parturient rises from a supine to a sitting position with hands clasped behind the head.

80% POWER She succeeds only by extending the arms.

60% POWER She can only lift the scapulae from the bed.

40% POWER She can only lift the shoulders.

20% POWER If only an increase in tension is felt during the effort.

Figure 1. Measuring the power of the rectus abdominalis muscle in the RAM test. The parturient is asked to come slowly to a sitting position when lying perfectly supine (no pillow, legs extended) on the bed. Reprinted with permission from Hodgkinson and Marx, eds. Obstet Anesth Digest 4;31–34;1984.

Table 2. Matched Results of the Bromage and RAM Blocks 20 Minutes after LEA in 20 Cesarean Sections

Bromage block (total $n = 20$)		RAM block (total $n = 20$) 0% Block ($n = 0$)	20% Block ($n = 1$)	40% Block ($n = 2$)	60% Block ($n = 10$)	80% Block ($n = 7$)	100% Block ($n = 0$)
0% Block	($n = 7$)	—	—	1	3	3	—
33% Block	($n = 9$)	—	—	—	6	3	—
66% Block	($n = 2$)	—	—	1	1	—	—
100% Block	($n = 2$)	—	1	—	—	1	—

ference between the RAM-tests before and after LEA. The first RAM-test was assessed before the injection of local anesthetic. Both the Bromage and the RAM-tests were performed 20 min after the injection of the local anesthetic and again at the completion of surgery (90–120 min after injection). In both test methods, asymmetric blocks were recorded as the degree of motor weakness observed on the more affected side.

Table 3. Matched Results of the Bromage and RAM Blocks After Surgery

		RAM block (total $n = 20$)					
Bromage block (total $n = 20$)		0% Block ($n = 0$)	20% Block ($n = 0$)	40% Block ($n = 3$)	60% Block ($n = 13$)	80% Block ($n = 4$)	100% Block ($n = 0$)
0% Block	($n = 9$)	—	—	1	7	1	—
33% Block	($n = 5$)	—	—	—	5	—	—
66% Block	($n = 5$)	—	—	2	1	2	—
100% Block	($n = 1$)	—	—	—	—	1	—

Table 4. Matched Results of the Bromage and RAM blocks in 20 Cesarean Sections

	A, 20 min after injection					*B*, After surgery			
	RAM block					RAM block			
Bromage block	0%	20–40%	60–80%	100%	Bromage block	0%	20–40%	60–80%	100%
0%		1	6		0%		1	8	
33%			9		33%			5	
66%		1	1		66%		2	3	
100%		1	1		100%			1	

The Spearman-rank correlation coefficient (9) was used to compare the results of the two tests. A value of $P < 0.05$ was considered the minimum level of statistical significance.

Results

The matched results of the RAM-block and the Bromage test are shown in Tables 2 and 3. The RAM-block was never zero in this study; none of the anesthetized women was able to reach the erect position. Seventeen women (85%) had a RAM-block of 60% or more at both determinations. On the other hand, the Bromage block was zero in seven women (35%) at the first determination and in nine (45%) at the second determination. Only two women (12%) had a Bromage block of 66% or more at the first determination (Table 2); and only four (24%) had a Bromage block of 66% or more at the second determination (Table 3).

If we compare the two tests we see that in six (86%) of the seven women with a zero Bromage block at the first determination (Table 3), the RAM-block was 60% or more. In eight (89%) of the nine women with a zero Bromage block at the second determination (Table 3), the RAM-block was 60% or more.

Discussion

Of the women with a zero motor block on the basis of the Bromage test, 86% had a RAM-block of 60% or more at the first determination and 89% at the second determination. Obviously the two tests do not correlate ($P > 0.05$).

To visualize the relationship between the two tests, we can group the results of the RAM-block in the following manner:

RAM-block 0% = no motor block
RAM-block 20–40% = mild motor block

RAM-block 60–80% = pronounced motor block
RAM-block 100% = complete motor block

and plot the results in two tables (Tables 4*A* and 4*B*). With a perfect correlation, all results should fall in the hatched part of the diagram.

In a segmental blockade it is not surprising that the two tests do not give comparable results because the Bromage test measures effects on nerve segments L-1–S-2 and the RAM-tests measures effects on nerve segments T-5–T-12. The T-5–T-12 segments innervate not only the rectus abdominalis muscle but the other abdominal wall muscles as well, including the internal and external oblique (T-8–T-12) and the transversalis (T-7–T-12).

Considerable motor blockade of the abdominal muscles is desirable in abdominal surgery, but motor blockade of the lower extremities is not required in these operations. We think that the RAM-test is a more appropriate test than the Bromage test in all situations where one is interested in evaluating the degree of abdominal muscle relaxation under LEA. The RAM-test may also be an appropriate test for comparing different local anesthetics, concentrations, and techniques in LEA for their effects on relaxation of the abdominal muscles. The RAM-test is an easy test and can be performed in less than 10 sec. The occurrence of hypotension or fetal distress in this short time is unlikely and was never seen by the authors.

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Lidocaine Enhances Intraoperative Ventricular Defibrillation

Carol L. Lake, MD, Irving L. Kron, MD, Robert M. Mentzer, MD, and
Richard S. Crampton, MD

LAKE CL, KRON IL, MENTZER RM, CRAMPTON RS. Lidocaine enhances intraoperative ventricular defibrillation. Anesth Analg 1986;65:337–400.

The efficacy of lidocaine during myocardial reperfusion in coronary artery bypass surgery was evaluated in 20 patients randomly assigned to a control group ($n = 10$) or to receive lidocaine, 1 mg/kg intravenously 5 min before aortic unclamping and cardiac reperfusion, followed by infusion at 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ($n = 10$). We recorded ECG leads II and V_5 continuously, and number, energy, and current of direct current (DC) shocks starting at 1 joule. The number of low energy DC shocks to sustained defibrillation (5.5 ± 2.0 vs 3.5 ± 2.0, mean ± SD, $P < 0.05$) decreased significantly with lidocaine infusion. The energy (11.0 ± 6.3 vs 5.6 ± 3.9 joules, $P < 0.05$) and current (12.7 ± 4.2 vs 8.9 ± 4.7 amperes, not significant) likewise decreased with lidocaine infusion. Energy and current for the first successful shock, although lower in the lidocaine group, were not statistically significantly lower than in the control group. Initial reperfusion rhythm was not influenced by lidocaine. Plasma electrolyte levels, arterial blood gas tensions, myocardial temperature, and surgical technique—factors known to influence defibrillation—were similar in all patients. Administration of lidocaine during myocardial reperfusion allows defibrillation with fewer DC shocks of lower energy and current.

Key Words: HEART, ARRHYTHMIAS—defibrillation. ANESTHESIA—cardiovascular. ANESTHETICS, LOCAL—lidocaine.

Ventricular defibrillation during cardiac surgery is influenced by factors such as the duration of reperfusion, arterial oxygenation, serum potassium, and perfusion pressure (1). This study evaluated the effects of antidysrhythmic plasma concentrations of lidocaine in humans during myocardial reperfusion and cardiopulmonary bypass at a time when myocardial temperature, serum potassium, and other factors were optimally controlled. Early investigators (2) noted that topical or systemic application of antidysrhythmic drugs controlled intraoperative dysrhythmias in experimental animals. More recent investigators have suggested that lidocaine promotes spontaneous defibrillation during the reperfusion phase of coronary artery bypass grafting (3,4).

Methods

Twenty-two patients undergoing coronary artery bypass grafting were prospectively assigned by a random number table to either the control group I ($n = 11$), in which no antidysrhythmic drug or other injection was given, or to group II ($n = 11$), in which lidocaine, 1 mg/kg was given intravenously 5 min before aortic unclamping and myocardial reperfusion into the central venous pressure catheter, followed by an infusion at 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The infusion of lidocaine was continued until the ventricles defibrillated. Only patients with no history of myocardial infarction or dysrhythmias within the preceding 6 months and with an ejection fraction greater than 0.5 by angiogram or echocardiography were included. Electrocardiograph leads II and V_5 were monitored continuously throughout surgery on a Hewlett–Packard oscilloscope (Waltham, MA), and were recorded from the time of aortic unclamping to defibrillation on a Hewlett–Packard Model 7758B recorder. Dysrhythmias after discontinuation of cardiopulmonary bypass or after operation were also noted. The study was performed between October 1983 and March 1985. It was approved by the Human Investigation Committee of the University of Virginia.

More than 30 hemodynamic, biochemical, tem-

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Address correspondence to Dr. Lake, Box 238, Department of Anesthesiology, University of Virginia, Charlottesville, VA 22908.

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Table 1. Reperfusion Rhythm

	Ventricular fibrillation (number of patients)	Other spontaneous rhythm (number of patients)
Group I (control)	4	6 not significant
Group II (lidocaine)	3	7

Table 2. Direct Current Shocks

	Group I (n = 10)	Group II (n = 9)	P
Energy (first successful shock, J)	6.6 ± 5.2	4.7 ± 4.0	ns
Energy (last successful shock, J)	11.0 ± 6.3	5.6 ± 3.9	0.05
Current (first successful shock, A)	9.3 ± 4.4	7.8 ± 4.7	ns
Current (last successful shock, A)	12.7 ± 4.2	8.9 ± 4.7	ns
Number of shocks to sustained defibrillation	5.5 ± 2.0	3.5 ± 2.0	0.05
Number of shocks to initial defibrillation	3.4 ± 1.8	2.7 ± 1.8	ns
Impedance (first successful shock, Ω)	25.3 ± 6.7	19.8 ± 5.4	ns
Impedance (last successful shock, Ω)	21.9 ± 6.8	18.7 ± 5.5	ns

Results are mean ± SD.
Abbreviations: J, joules; A, amperes; Ω, ohms; ns, not significant.

poral, or thermal variables important to defibrillation were measured or recorded (1). These include plasma concentrations of potassium, norepinephrine, epinephrine, and ionized calcium; mean systemic and pulmonary arterial pressures, coronary perfusion pressure, and systemic vascular resistance; arterial P_{O_2}, P_{CO_2}, and pH; duration of myocardial ischemia, reperfusion, and cardiopulmonary bypass; and myocardial, esophageal, arterial, and venous temperatures. Intravascular pressures were measured using Bentley Trantec Model 800 transducers (Bentley Laboratories, Irvine, CA) and Hewlett–Packard pressure modules (Waltham, MA) calibrated against a mercury column. Coronary perfusion pressure was defined as the difference between mean arterial and mean pulmonary arterial pressure during cardiopulmonary bypass. Plasma potassium was measured using a Nova Biomedical direct potentiometer (Waltham, MA). Plasma concentration of ionized calcium was determined on an SS20 analyzer (Orion Biomedical, Cambridge, MA). Norepinephrine and epinephrine were measured in plasma using high-performance liquid chromatography (5). Arterial blood gas tensions and pH were measured using standard electrodes. Myocardial temperature was determined by measurement of the interventricular septal temperature using a Wilton Industries myocardial probe. Perfusion temperature was measured with an in-line thermistor in the arterial return from the oxygenator (during extracorporeal circulation). The plasma concentration of lidocaine was measured using gas chromatography with a flame ionization detector. Mepivacaine was used as an internal standard. This method is linear between 0.08 and 9.5 micrograms of lidocaine (6).

Biochemical variables were measured in mixed venous blood obtained at the venous port of the oxygenator at spontaneous resumption of cardiac rhythm or immediately before the first shock attempt and after defibrillation. Hemodynamic, temporal, and thermal variables were noted at the time of each shock. The incidence of myocardial infarction, left ventricular failure (defined as the triad of a pulmonary wedge pressure or left atrial pressure greater than 18 torr, a cardiac index below 2.2 $L \cdot min^{-1} \cdot m^{-2}$, and a systolic arterial pressure below 90 torr), or the need for antiarrhythmic, vasodilator, or inotropic drugs after cardiopulmonary bypass and surgery were noted.

Direct current (DC) shocks, starting at 1 joule (J) were delivered by a Series 640 defibrillator (Physio Control, Redmond, WA) if a cardiac rhythm did not return spontaneously and if the myocardial septal temperature was more than 26°C. The specific timing of defibrillation was determined by the surgical requirement for a beating heart to prevent ventricular distention in unvented hearts after aortic unclamping. If the initial shock was unsuccessful, the energy of the second shock was increased to 2.5 J. Thereafter, energy was increased by 2.5 J until defibrillation was achieved. A set of 88-mm diameter concave electrodes was placed at the apex of the left ventricle and at the base of the right ventricle, the positions where defibrillation can be accomplished with the lowest current (7). To prevent myocardial damage from increased energy or current, lidocaine, 100 mg, was given intravenously to control patients who failed to defibrillate after more than 8 low-energy DC shocks or a single shock of 20 J (after a sequence of shocks of 1, 2.5, 5, 7.5, 10, and 15 J energy). Peak delivered current was measured with a P6303 current probe and amplifier (Tektronix, Inc., Portland, OR). All patients received cardioplegia with Plegisol® (sodium 120 mEq/L, potassium 15 mEq/L, magnesium 32 mEq/L, calcium 2.4 mEq/L, chloride 160 mEq/L, bicarbonate 10 mEq/L) at 28°C using a Sarns S10K Blood Pump for cardioplegia delivery (MARA, Ann Arbor, Michigan). Myocardial temperature ranged from 10 to 15°C during aortic occlusion. Anesthetic agents used included halothane, isoflurane, fentanyl, or sufentanil, alone or in combination with nitrous oxide. Statistical

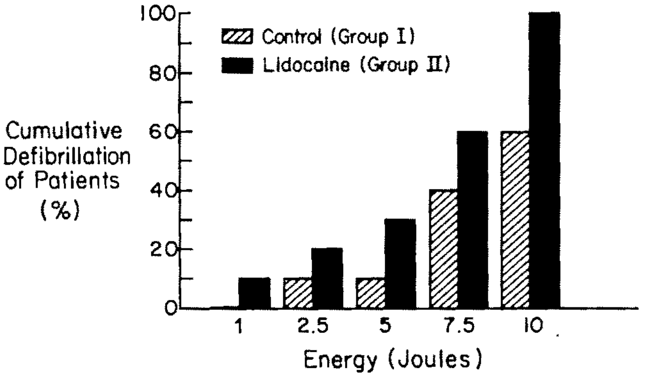

Figure 1. The cumulative percent of patients permanently defibrillated at each energy level is shown. One patient in the lidocaine group required no DC shocks.

analysis was performed using Student's *t*-test or χ^2-test, with $P < 0.05$ taken as statistically significant.

Results

All patients received both β-adrenergic and calcium entry blockers on the morning of surgery with the exception of two patients, one in group I who received only verapamil and one in group II who received only propranolol. There were no differences between groups in severity of coronary disease or surgical procedure. Group I had 2.5 ± 0.5 grafts per patient, and group II 2.3 ± 0.5. In group II the mean lidocaine concentration was 2.36 ± 0.80 μg/ml with administration for 7.2 ± 6.8 min prior to DC shocks. Two patients were eliminated from the study, one because the arterial P_{O_2} was < 70 torr at defibrillation (group I) and the other because lidocaine was administered only after aortic unclamping, rather than both prior to and after unclamping (group II). In each group, four patients received isoflurane, four halothane, and two fentanyl or sufentanil as the principal anesthetics.

The prevalence of ventricular fibrillation (VF) on aortic unclamping was similar in both groups (Table 1). The majority of patients with spontaneous nonfibrillatory rhythms in both groups had asystole (5 of 7 in group II, 5 of 6 in group I), whereas one patient in each group was in complete heart block and one patient in group II had idioventricular rhythm. Only one patient (lidocaine group) spontaneously developed a normal rhythm and did not require DC shock. Both energy and the number of shocks required for sustained defibrillation were lower in group II than group I. A 50% success rate for shocks occurred at 5 J in the lidocaine group, but not until 10 J in the control group. However, neither the energy nor current of the first successful shock differed between groups. A similar number of shocks to initial defibrillation were required in both groups (Table 2). There were no significant differences in the cumulative percentage of patients defibrillated at any particular energy level. All patients in group II defibrillated at 10 J or less (Fig. 1). Myocardial impedance was lower in the lidocaine-treated group both at initial defibrillation attempt and at the time of the last shock. Impedance also decreased from first to last shock, as has been noted previously with transthoracic defibrillation (8) (Table 2).

Table 3. Hemodynamic, Biochemical, Thermal, and Temporal Variables at Last Shock

	Group I (n = 10)	Group II (n = 9)	P
Mean arterial pressure (torr)	58 ± 11	53 ± 9	ns[a]
Mean pulmonary pressure (torr)	7 ± 5	10 ± 4	ns
Coronary perfusion pressure (torr)	50 ± 13	44 ± 9	ns
Systemic vascular resistance (dynes·cm·sec^{-5})	755 ± 196	664 ± 174	ns
pH (units)	7.35 ± 0.05	7.37 ± 0.04	ns
P_{CO_2} (torr)	42 ± 7	40 ± 5	ns
P_{O_2} (torr)	244 ± 106	266 ± 83	ns
Epinephrine (ng/ml)	762 ± 831	332 ± 325	ns
Norepinephrine (ng/ml)	1009 ± 609	733 ± 537	ns
Potassium (mEq/L)	5.0 ± 0.6	4.8 ± 0.6	ns
Calcium ion (mEq/L)	1.96 ± 0.1	1.96 ± 0.1	ns
Myocardial temperature (°C)	36.9 ± 1.3	35.2 ± 3.1	ns
Reperfusion time to defibrillation (min)	6.3 ± 1.8	4.5 ± 3.2	ns
Duration bypass to defibrillation (min)	58 ± 15	50 ± 13	ns
Ischemic time (min)	47 ± 15	43 ± 13	ns

Results are mean ± SD. [a]ns, not significant.

Redevelopment of VF after successful DC shock occurred less frequently in the lidocaine-treated patients (1.3 ± 1.6 vs 2.0 ± 2.3 episodes per patient) although it was not a statistically significant difference. No differences were noted in plasma electrolyte levels, arterial blood gas tensions, myocardial temperature, plasma catecholamine levels, or coronary perfusion pressure at sustained defibrillation (19 patients) or spontaneous resumption of cardiac activity without defibrillation (one patient) (Table 3). Plasma catecholamines were increased in all patients, and no attempt to relate the levels to either the shock energy required or the occurrence of dysrhythmias was made. The myocardial temperature was higher, reperfusion time longer, and systemic vascular resistance greater in the control group, although not statistically significantly different than in patients given lidocaine. Three patients in the control group eventually received lidocaine when VF could not be terminated after the 20 J shock or more than eight lower-energy DC shocks. Shocks given after lidocaine administration to the control group were excluded from statistical analysis. All patients defibrillated. No differences in the occurrence of atrial or ventricular dysrhythmias or the need for antiarrhythmic drugs after discontinuation of bypass or after operation were noted, as lidocaine was discontinued immediately after defibrillation. The frequency of myocardial infarction, cardiac failure, and the need for inotropic or vasodilator drugs were similar in both groups.

Discussion

Factors previously recognized as significant determinants of intraoperative ventricular defibrillation with low energy shocks include levels of serum potassium and ionized calcium, arterial oxygenation, coronary perfusion pressure, oxygenation, reperfusion time, coronary myocardial temperature, and systemic vascular resistance (1). Of these factors, potassium is of paramount importance because a high plasma potassium level may chemically cause defibrillation (7) as well as decreases in the experimental defibrillation threshold (9). The concentration of serum potassium in all our patients was well within the range of values previously noted to be associated with successful DC shocks (1). Likewise, the increased levels of plasma catecholamines in our patients do not contribute to myocardial damage (12), but may have accentuated dysrhythmogenesis.

Lidocaine blocks the fast sodium channel in the cell membrane. It also suppresses phase 4 of abnormal spontaneous cellular membrane depolarization by increasing outward potassium conductance in ventricular tissue. The diastolic threshold to ventricular stimulation is increased, thus increasing the current required to induce a premature ventricular contraction. Thus lidocaine inhibits dysrhythmias caused by enhanced automaticity or ectopic foci.

The initial reperfusion rhythm was not normalized by therapeutic plasma concentrations of lidocaine during reperfusion as previously reported (3). Our failure to confirm this observation may have resulted from differences in the duration of reperfusion permitted before DC shock, the timing, and the method of lidocaine administration. Because lidocaine increases ventricular fibrillation threshold in humans (10), fewer shocks were required, as noted by other investigators (4), because VF did not recur after successful shocks. The lower myocardial resistance noted in lidocaine-treated patients may also have affected the intramyocardial spread of current and facilitated defibrillation.

A dose-dependent increase in the defibrillation threshold has been reported in canine experiments during lidocaine administration (11,13). However, the plasma levels in our patients were below the 3 μg/ml concentration reported to increase the experimental canine defibrillation threshold (13). Thus at human therapeutic plasma concentrations, a clinically important increase in defibrillation threshold appears unlikely. Recent studies in animals (14) describe net lactate production and norepinephrine release in the myocardium after only two 30-J DC shocks, suggesting both derangement of myocardial metabolism and regional myocardial perfusion.

In summary, our study suggests that prophylactic administration of lidocaine during myocardial reperfusion would permit defibrillation with fewer DC shocks of lower energy.

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Resuscitation from Bupivacaine-Induced Cardiovascular Toxicity During Partial Inferior Vena Cava Occlusion

Gregory W. Kasten, MD, and Stuart T. Martin, MD, PhD

KASTEN GW, MARTIN ST. Resuscitation from bupivacaine-induced cardiovascular toxicity during partial inferior vena cava occlusion. Anesth Analg 1986;65:341–4.

The hemodynamic effects and ability to resuscitate animals experiencing bupivacaine cardiovascular toxicity after partial inferior vena cava occlusion were investigated in anesthetized dogs ($n = 12$). Partial occlusion of the inferior vena cava resulted in a 12% decrease in mean arterial pressure, a 62% decrease in cardiac output, a 66% decrease in stroke volume, and a 135% increase in systemic vascular resistance.

Bupivacaine, 20 mg/kg intravenously, resulted in cardiovascular collapse in all animals. The resuscitation time for animals without partial caval occlusion was 2.1 ± 0.5 min, whereas that for animals with partial caval occlusion was 22.2 ± 6.9 min ($P < 0.05$). Significantly increased amounts of epinephrine and $NaHCO_3$ were required to resuscitate the animals with caval occlusion. We conclude that partial inferior vena cava occlusion can significantly alter the ability to resuscitate animals experiencing bupivacaine cardiovascular toxicity.

Key Words: ANESTHETICS, LOCAL—bupivacaine. ANESTHESIA—obstetric. TOXICITY—bupivacaine.

There has been considerable concern regarding the untoward cardiovascular effects after accidental intravenous administration of the potent amide local anesthetics bupivacaine and etidocaine. Recent editorials describe a preponderance of these toxic cardiovascular events in otherwise healthy parturients scheduled for caesarean section with epidural administration of bupivacaine (1,2,3). An important factor that must be considered when attempting to resuscitate the parturient is vena cava compression by the gravid uterus. We recently reported that resuscitation after massive intravenous doses of bupivacaine in anesthetized well-hydrated dogs can be done consistently and quickly (4). Because the results of our investigation are at variance with the apparent difficulty of resuscitation in parturients, this investigation was conducted to examine whether or not vena cava obstruction interferes with the ability to resuscitate an animal after intravenous administration of cardiovascular toxic doses of bupivacaine.

Methods

Twelve adult mongrel dogs weighing 21.6 ± 3.5 kg were anesthetized with intravenous sodium pentobarbital, 30 mg/kg, and were immobilized with pancuronium bromide, 0.15 mg/kg. A cuffed endotracheal tube was inserted, and the animals were ventilated with 100% oxygen (AirShields® ventilator). Tidal volume, respiratory rate, and sodium bicarbonate administration (0.5–1 mEq/kg at least 30 min prior to the experimental period) were adjusted to provide the following arterial blood gas values: pHa 7.35–7.45, Pa_{CO_2} 32–40 mm Hg, and Pa_{O_2} 300–500 mm Hg. Arterial blood gas values were also measured after vena cava partial occlusion.

A left femoral arterial catheter was inserted to obtain arterial blood for measurement of gas tensions and for direct recording of arterial blood pressure. Using the right femoral vein, a Swan–Ganz catheter (American Edwards model 93-131-7F) was placed into the pulmonary artery. Cardiac output was measured using the thermodilution technique and a cardiac output computer (American Edwards model 9520A). Each time the cardiac output was determined, five values were obtained and the results were averaged. A lead II surface ECG, arterial blood pressure, right atrial pressure, and pulmonary artery pressure were recorded continuously on a polygraph (Grass model 7A). A sternotomy and pericardiotomy were per-

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Address correspondence to Dr. Kasten, Department of Anesthesiology, University of Kentucky Medical Center, Lexington, Kentucky 40536-0084.

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Table 1. Hemodynamic Effects of Partial Inferior Vena Cava Occlusion in Dogs

Parameter	Baseline	Partial Occlusion
Mean arterial pressure (mm Hg)	132 ± 10	116 ± 15^a
Cardiac output (L/min)	3.2 ± 0.8	1.2 ± 0.4^a
Stroke volume (ml/beat)	22.3 ± 5.1	7.5 ± 3.4^a
Heart rate (beat/min)	143 ± 8	159 ± 16^a
Central venous pressure (mm Hg)	8.1 ± 2.0	6.0 ± 1.5^a
Pulmonary artery pressure (mm Hg)	15.9 ± 3.1	11.0 ± 2.1^a
Pulmonary capillary wedge pressure (mm Hg)	8.3 ± 1.9	5.0 ± 1.9^a
Pulmonary vascular resistance (cm·sec^{-1}·dynes^{-5})	165 ± 18	401 ± 111^a
Systemic vascular resistance (cm·sec^{-1}·dynes^{-5})	3108 ± 950	7333 ± 2450^a
	mean ± SD	mean ± SD

$n = 6$.
$^aP < .05$ from control.

Table 2. Resuscitation Time and Drugs Required

	Control	Clamped
Resuscitation time (min)	2.1 ± 0.5	22.2 ± 6.9^{a,c}
Epinephrine dose (mg)	1.3 ± 0.4	7.1 ± 2.5^{b,c}
NaHCO$_3$ dose (mEq)	22.4 ± 4.5	45.9 ± 10.1^{b,c}
Survivors	6/6	5/6
	Mean ± SD	Mean ± SD

$^an = 5$.
$^bn = 6$.
$^cP < 0.05$ between groups.

formed to expose the epicardial surface of the heart after an additional intravenous 10 mg/kg of pentobarbital.

The experimental protocol was as follows: after animal preparation, there was a 30-min baseline period during which lead II surface ECG, systemic arterial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, central venous pressure, and cardiac output were determined. Systemic vascular resistance, pulmonary vascular resistance, and stroke volume were calculated from these data. After collection of data during this baseline period, a partial occluding clamp was placed on the inferior vena cava just below where it passed through the diaphragm. The clamp was adjusted in such a way that the pulmonary capillary wedge pressure decreased by approximately 50%; the inferior vena cava was not completely occluded. The animal was then observed for several minutes to ascertain the stability of the new pulmonary capillary wedge pressure. A 20-min period was then allowed to elapse with the clamp in place, at the end of which hemodynamic parameters were again measured.

Bupivacaine was administered after the second set of data were obtained in a dose of 20 mg/kg over 60 sec intravenously into the right atrium in six animals with the vena cava partially clamped and in six control animals with no vena cava occlusion. The protocol for resuscitation of the animals was as follows: after cardiac arrest, controlled ventilation with oxygen at an F_{IO_2} of 1.0 was continued. Open chest cardiac massage was performed to allow for good circulation of administered drugs. Intravenous epinephrine was administered at a dose of 1.0 mg every 3 min, and sodium bicarbonate was given at a dose of 1 mEq/kg at the beginning of resuscitation and again 15 min later if arterial blood gas analysis revealed a metabolic acidosis. The time from beginning of resuscitation until return to baseline blood pressures was recorded. Data analysis was done using Student's *t*-test for paired data for hemodynamic alterations after cava clamping, and analysis of variance and Student's *t*-test for unpaired data for resuscitation results between the clamped and unclamped groups. $P < 0.05$ was considered statistically significant.

Results

There was no significant difference between the baseline hemodynamic parameters in the control and clamp groups. Partial occlusion of the inferior vena cava resulted in a slight decrease in mean arterial pressure and much greater decreases in cardiac output and stroke volume (Table 1). This was accompanied by a significant reflex increase in systemic vascular resistance.

The administration of bupivacaine, 20 mg/kg, resulted in cardiovascular collapse in each animal and was preceded by progressive bradycardia and finally asystole. No animal sustained ventricular tachyarrhythmias. All six animals were quickly resuscitated in the unclamped group, but only five of six animals could be resuscitated after a much longer time in the clamped group (Table 2). The resuscitation time of 22.2 ± 6.9 min in the clamped group is for the five animals that could be resuscitated; the one animal that could not be resuscitated in the clamped group is not included in this value. Statistically significant increased doses of epinephrine and sodium bicarbonate were required in the clamped group during resuscitation (Table 2).

Discussion

We recently reported that after massive intravenous bupivacaine overdosage in well-hydrated anesthetized dogs, successful cardiovascular resuscitation can be accomplished easily and consistently (4). Anecdotal cases of bupivacaine cardiovascular toxicity report difficult and sometimes impossible resuscitation attempts (1,2,3) that our current findings do not substantiate. Many of these case descriptions occurred in parturients. The reason for a clustering of these problems in the parturient is uncertain at this time. Possible factors that could make intravenous administration of bupivacaine more likely and resuscitation more difficult in parturients include the following: 1) ease of intravenous cannulation during epidural placement; 2) inadequate anesthetist preparation for cardiopulmonary resuscitation; 3) increased oxygen consumption of mother and fetus; 4) physiologic alteration during pregnancy, such as increased progesterone serum levels that might render the patient more susceptible to cardiovascular depression from bupivacaine; and 5) inferior vena cava compression by the gravid uterus.

Several of these factors have been described. Epidural veins are greatly dilated late in pregnancy because they become one of the major collateral channels for lower extremity venous return in the presence of a gravid uterus that partially obstructs the inferior vena cava. Thus intravenous cannulation during epidural placement can easily occur. Maternal oxygen consumption increases and functional residual capacity decreases during pregnancy (5). These combine to render the parturient hypoxic quickly during apnea. The importance of having adequate resuscitative drugs and equipment immediately at hand cannot be stressed enough. Evidence has been reported demonstrating an inconsistent change in bupivacaine sensitivity in the pregnant vs non-pregnant animal (6,7). A particularly important factor that has not been completely investigated and may partly explain the difficult resuscitation in parturients is inferior vena cava obstruction in the supine position due to the pressure of the gravid uterus.

Postural vena cava occlusion and the supine hypotensive syndrome in late pregnancy were first described in 1952 by Howard et al. (8). Several parturients were noted to display marked variations in blood pressure when they were supine and then moved to a position of lying on their left side. Associated with the decrease in blood pressure in the supine position were tachycardia, diaphoresis, and occasional loss of consciousness (8). Several subsequent investigations documented nearly complete vena cava occlusion due to the uterus compressing the vena cava in the supine position (9,10). An invasive hemodynamic study in parturients demonstrated that vena cava occlusion resulted in decreased right atrial pressure, decreased cardiac output, and a reflex increase in systemic vascular resistance (11). The decreased cardiac output and increased systemic vascular resistance with reduced organ and regional perfusion can have dramatic effects on drug pharmacokinetics. In animals, decreased local anesthetic clearance was found when the animals were volume-depleted (12). Discrepancies between lower and upper extremity thiopental concentrations in parturients have been attributed to vena cava occlusion and altered volume of distribution of thiopental (13). Compression of vena cava with resultant altered volume of distribution of a drug could be expected to result in higher serum levels and consequently the exposure of the maternal heart and the fetus to higher blood levels of these drugs. Thus not only can vena cava occlusion affect cardiac performance, but it can also profoundly alter pharmacokinetic parameters.

In our animals, partial occlusion of the vena cava resulted in only a minor decrease in mean arterial pressure. For the clinician not using invasive hemodynamic monitoring the situation would appear reasonably stable. However, the apparent stability is falsely reassuring because blood pressure is maintained by a doubling of systemic vascular resistance in the face of a greatly reduced cardiac output. These hemodynamic effects of vena cava occlusion could have profound physiologic implications. Besides the direct cardiac effects of decreased filling pressure and cardiac output, regional blood flow, and especially liver blood flow, could alter drug distribution and metabolism. Although we did not measure bupivacaine serum concentrations, it is likely that higher bupivacaine serum concentrations occurred over a longer period of time in the vena cava occluded group.

This study indicates that the degree of venous return and subsequent effect on cardiac output, regional perfusion, and pharmacokinetics are important determinants of the ability to resuscitate dogs given intravenous cardiovascular toxic doses of bupivacaine. The particular difficulty in resuscitation of the parturient patients may be explained, at least in part, by these findings. The most important aspect of this problem is the prevention of intravascular injection of potent amide local anesthetics. However, should an accidental intravenous administration of bupivacaine occur and result in cardiovascular collapse, the cardiopulmonary resuscitation effort must include displacement of the uterus off the vena cava. If lateral displacement by tilt fails, then prompt consideration should be given to emergency caesarean section. A case report has documented that after a cardiac arrest, a mother could not be resuscitated until after a caesarean section was performed and the fetus removed (14). Thus this technique could be life saving.

In summary, this study demonstrates that partial vena cava occlusion can have dramatic effects on the ability to resuscitate animals bupivacaine-induced cardiovascular collapse. These results may explain the apparent difficulty in resuscitating parturients after accidental intravenous administration of potent amide local anesthetics. We believe that should this untoward event occur clinically, prompt relief on the caval obstruction may be life-saving.

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A Microelectrode Study of the Effects of Atracurium on Neuromuscular Transmission

Tetsutaro Otagiri, MD, and Martin D. Sokoll, MD

OTAGIRI T, SOKOLL MD. A microelectrode study of the effects of atracurium on neuromuscular transmission. Anesth Analg 1986;65:345–9.

Using standard microelectrode recording techniques, we studied the effects of atracurium on neuromuscular transmission in a concentration range between 10^{-13} *and* 10^{-5} *M in the rat diaphragm. Both intact and cut diaphragm preparations were used. Atracurium produced no significant alteration of miniature endplate potential (MEPP) frequency* ($P > 0.05$)*. Increasing concentrations of atracurium* (10^{-6}–10^{-5} *M) caused a linear decrease in MEPP amplitude from 70.5 ± 2.3% to 28.0 ± 2.5% of baseline levels* ($P < 0.05$)*. In the cut diaphragm preparation, atracurium increased the degree of rundown and decreased quantum content of the endplate potential (EPP). The above observations suggest that atracurium interferes with neuromuscular transmission by, first of all, producing cholinergic receptor block and secondly, producing frequency-dependent inhibition of release of acetylcholine from the nerve terminal.*

Key Words: NEUROMUSCULAR RELAXANTS—atracurium.

Though neuromuscular blocking agents were initially thought to have as their sole site of action the postsynaptic membrane in blocking the cholinergic receptor (1), at least part of the activity of many of these drugs is now recognized to be the decrease of release of acetylcholine from the motor nerve terminal (2–5). In addition, the type of action of neuromuscular relaxants is influenced by the concentration used. Small concentrations have stimulating properties whereas larger concentrations produce blockade (4).

Atracurium is a recently developed neuromuscular blocking agent now available for clinical use. In experimental animals, the drug produced blockade of the indirectly stimulated muscle. In the chick biventer cervicis muscle, the drug produced no contracture, suggesting absence of nicotinic agonist activity (6). These findings indicate that atracurium is a nondepolarizing neuromuscular blocking drug. The absence of drug-induced contracture in the biventer cervicis, an action characteristic of the agonistic property of succinylcholine, suggests that atracurium has little or no succinylcholine-like activity and should produce no fasciculations or potassium release after administration. This study proposed to examine the effects of a wide range of concentrations of atracurium on various indicators of acetylcholine release from the nerve terminal and postsynaptic receptor sensitivity.

Materials and Methods

All experiments were carried out in vitro at room temperature on the rat diaphragm (19–22°C). The preparation was mounted in a lucite bath of 3 ml volume, the bottom of which was lined with plastic in which was embedded a plano-convex lens. The muscle was constantly perfused (flow rate 7 ml/min) with Ringer's solution modified for the rat (NaCl 137, KCl 5.0, Na_2HPO_4 1.0, $NaHCP_3$ 14.8, $MgCl_2$ 1.0, $CaCl_2$ 1.0, and dextrose 11 mmol/L. The solution was constantly bubbled with 95% oxygen/5% carbon dioxide. In all preparations, each endplate served as its own control. Control readings of the property being studied were obtained. The specific concentration of atracurium being studied was then applied for 15 min at a bathing solution flow rate of 7 ml/min. Test values of the property under study were then obtained. The preparation was then washed for 30 min at the same flow rate and, if the resting membrane potential was unchanged (± 3 mV) from control values, new control readings were obtained for the next drug concentration.

Intracellular potentials were measured with glass capillary microelectrodes of 10–20 mΩ resistance filled with 3M KCl in a conventional manner (4). Miniature endplate potentials (MEPPs) were monitored on an

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Address correspondence to Dr. Sokoll, Department of Anesthesiology, University of Iowa Hospital, Iowa City, IA 52242.

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oscilloscope and recorded with either an Elema-Schonander mingograph 81 or photographed on moving film. Endplate regions were located by identifying MEPPs with an increase time of less than 1 msec.

Studies of MEPP amplitude and frequency were performed using the intact diaphragm. Control measurements were made for a period of 3 min, after which the concentration of drug to be studied was applied for a minimum of 15 min with a drug flow rate of 7 ml/min. After drug application, the parameters under study were again recorded. To determine frequency, MEPPs were counted over a period of 3 min. To determine mean MEPP amplitude a minimum of 100 MEPPs were measured. Resting membrane potential was observed for alterations during drug application.

To determine sensitivity of the postsynaptic cholinergic receptor, acetylcholine was ionophoretically applied to the end plate region (6,7). To minimize the effects of variability of size of the opening of different acetylcholine pipettes, the same pipette was used for both control and test determinations. Endplate sensitivity was expressed as millivolts of membrane depolarization per Coulomb × 10^{-9} current used to apply the acetylcholine.

The ability of the muscle cell membrane to generate an action potential was studied (8). Two microelectrodes were inserted into the same cell: one to deliver a depolarizing current, the other to record membrane potential change. The action potentials were analyzed for threshold, peak height, and rate of increase of the action potential. The rate of increase was determined with a resistance-capacitance circuit. Input resistance was determined by delivering hyperpolarizing pulses through the current-passing electrode, and the potential change was then compared to the quantity of current delivered (8).

The cut diaphragm preparation described by Barstad and Lilleheil (9) was used to study the effect of atracurium on neurally evoked acetylcholine release. Use of this preparation for neuromuscular studies has been supported by the work of Magelby et al. (10). The phrenic nerve was stimulated at frequencies of 0.1, 2, and 15 Hz.

Each experiment was performed on a single neuromuscular junction. Mean MEPP amplitude was first determined. Trains of endplate potentials (EPPs) were then elicited at the above frequencies. MEPP and EPP amplitudes were corrected for changes in membrane potential and EPP amplitudes were corrected for nonlinear summation (10,11).

Quantum content (m) of the EPP was obtained by dividing the corrected EPP amplitude by the corrected MEPP amplitude. Quantum contents were compared before and after application of atracurium for the first EPP of the train and the mean amplitude of the last 15 EPPs.

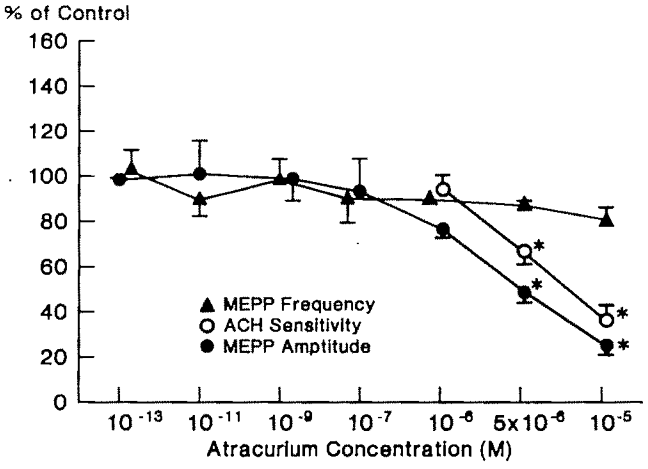

Figure 1. Effect of increasing concentrations of atracurium on MEPP amplitude and frequency and endplate sensitivity. Endplate sensitivity was determined only at the concentrations graphed. n = 10 endplates. Values are mean ± SEM. * = $P \leq 0.05$.

Statistics

Significance of dose–response relationships was tested using either analysis of a variance of Student's t-test as appropriate (12). Values were considered statistically significant when $P \leq 0.05$.

Results

Resting membrane potential was unaltered by the application of all concentrations of atracurium. MEPPs were recorded from ten endplates at each concentration of drug. A total of 32 endplates were studied in 28 muscles with ten endplates at each drug concentration. Miniature endplate potential amplitude was essentially unaffected between concentrations of 10^{-13}–10^{-7} M (Fig. 1). At a concentration of 10^{-6} M atracurium, the mean MEPP amplitude decreased to 70.5 ± 2.3% of the control. With atracurium at concentrations of 5×10^{-6} and 10^{-5}, MEPP amplitude was decreased to 48 ± 3.5 and 28 ± 2.5% of the control, respectively. MEPP frequency was unaffected over the entire concentration range of 10^{-13}–10^{-5} M (Fig. 1, Table 1).

The effects of atracurium on endplate sensitivity to ionophoretically applied acetylcholine were studied

Table 1. EPP and MEPP Values

Atracurium concentration	Frequency of stimulus and EPP quantum content			MEPP	
	0.1 Hz	2 Hz	15 Hz	Amplitude (mV)	Frequency (MEPP/sec)
Control	288 ± 31	336 ± 14	293 ± 13	0.482 ± 0.051	0.637 ± 0.055
10^{-13} M	311 ± 28	286 ± 17	270 ± 15	0.475 ± 0.043	0.659 ± 0.056
Control	353 ± 36	360 ± 34	391 ± 38	0.463 ± 0.062	0.683 ± 0.052
10^{-11} M	328 ± 52	291 ± 32	356 ± 33	0.468 ± 0.071	0.617 ± 0.046
Control	327 ± 27	358 ± 10	330 ± 28	0.473 ± 0.051	0.774 ± 0.043
10^{-9} M	301 ± 23	282 ± 15	299 ± 24	0.468 ± 0.043	0.717 ± 0.058
Control	467 ± 31	428 ± 26	451 ± 55	0.495 ± 0.081	0.846 ± 0.077
10^{-7} M	444 ± 21	333 ± 19	401 ± 49	0.462 ± 0.069	0.766 ± 0.079
Control	382 ± 43	402 ± 37	408 ± 37	0.502 ± 0.031	0.935 ± 0.071
10^{-6} M	362 ± 45	334 ± 35	359 ± 29	0.360 ± 0.024	0.768 ± 0.043
Control	401 ± 31	389 ± 22	420 ± 38	0.461 ± 0.033	0.857 ± 0.044
5×10^{-6} M	392 ± 28	276 ± 19	239 ± 26[a]	0.220 ± 0.014[a]	0.782 ± 0.031
Control	375 ± 22	370 ± 27	347 ± 83	0.488 ± 0.023	0.911 ± 0.056
10^{-5} M	345 ± 27	207 ± 18[a]	78 ± 20[a]	0.150 ± 0.005[a]	0.729 ± 0.037

Absolute values for MEPP amplitude and frequency and quantum content of EPP at progressive drug concentrations of atracurium. $n = 10$ endplates for MEPP amplitude and frequency and 7 for quantum content at each drug concentration.

[a] $P \le 0.05$ compared to control value.

in 17 endplates of 15 muscles with ten endplates studied at each drug concentration (Fig. 1). Sensitivity was unaffected at a concentration of 10^{-6} M and then decreased in a dose-related manner similar to the changes seen with respect to MEPP amplitude. Atracurium produced no significant alteration in muscle cell membrane input resistance or action potential generating properties.

The effects of atracurium on the process of acetylcholine release from the nerve terminal were examined using the cut diaphragm preparation. Recordings were made at seven endplates at each drug concentration studied. MEPPs and EPPs were recorded and amplitudes corrected to compensate for alterations in membrane potential. EPP amplitudes were also corrected for nonlinear summation. Quantum content was then calculated.

In the control (without drug) observations, no significant change ($P > 0.05$) occurred in the quantum content of the first EPP of a train compared to the mean value of the last 15 EPPs at any of the three stimulus frequencies. With the addition of atracurium, a decrease in the mean quantum content of the last 15 EPPs, when compared to the first EPP, was noted at stimulation frequencies of 2 and 15 Hz ($P < 0.05$) at drug concentrations of 5×10^{-6} and 10^{-5} M (Fig. 2, Table 1).

Discussion

Microelectrode techniques have long been utilized in the study of neuromuscular transmission. The earliest studies involved analyses of MEPP amplitude and frequency and their alteration by drugs. In these studies, drug-induced changes in MEPP frequency were interpreted as suggesting a presynaptic or nerve terminal effect of the drug, whereas changes in MEPP amplitude were accepted as drug-induced effects on the postsynaptic cholinergic receptor (13). These general concepts are still considered to be valid, though more limited in their interpretation because of the differences between spontaneous and induced transmitter release.

The technique used here necessitates mathematical corrections for both membrane potential changes and nonlinear summation. Despite these shortcomings, this technique has been used to analyze for drug actions on the nerve terminal and endplate by many investigators (5,9,14,15), and appears to be useful in studies reported here.

The absence of drug-induced alteration of resting membrane potential supports the concept that atracurium has little or no agonist activity. Similarly, the absence of changes in MEPP frequency suggest that atracurium has little effect on those processes gov-

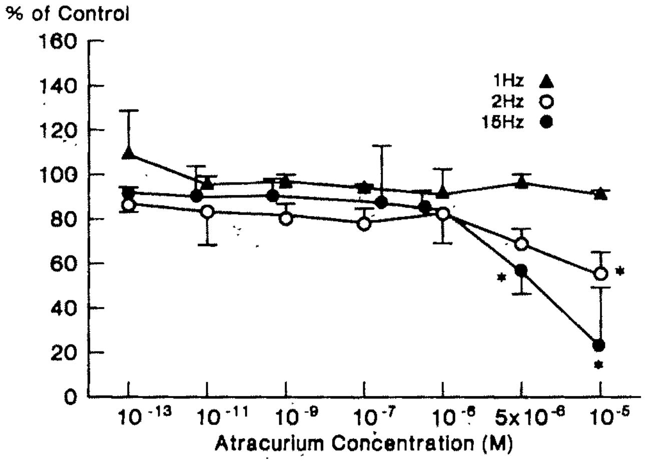

Figure 2. Effect of increasing concentrations of atracurium and increasing stimulation rate on EPP quantum content. Values are mean ± SEM. $n = 7$ endplates. * = $P \leq 0.05$.

erning spontaneous transmitter release. The presence of a dose-related decrease in both MEPP amplitude and endplate sensitivity to ionophoretically applied acetylcholine strongly suggest a significant depressant effect on the postsynaptic cholinergic receptor. These properties are similar to those of *d*-tubocurarine and pancuronium, but not gallamine (4,5,10,16,17). Both *d*-tubocurarine and pancuronium cause alterations in MEPP frequency not seen with atracurium.

The maximal rate of phrenic nerve stimulation used here was 15 Hz compared to 50 Hz or even 150 Hz sometimes used in this type of study. The nerve axon is able to tolerate the highest rates of stimulation. Muscle membrane, and particularly the junctional apparatus, can tolerate only lower rates of stimulation. The function of the rapid rates of stimulation is to stress neuromuscular transmission, particularly the presynaptic component. The change looked for, suggesting a degree of presynaptic failure, is a decrease in the quantum content of the EPP. Previous studies have demonstrated that this type of failure can be elicited with stimulation rates as low as 2 Hz. Our rate of 15 Hz, therefore, should be fast enough to document drug-induced interference with the presynaptic components of transmission (5).

Atracurium in concentrations of 5 × 10^{-6} M and greater had a significant depressant action on induced transmitter release in that the mean quantum content of the last 15 EPPs at 2 and 15 Hz was decreased compared to that of the first EPP. The mechanisms underlying this process have not been investigated here. The presence of presynaptic receptors and the action of drugs on these receptors has been the subject of a number of recent investigations (4,5,9). A possible relationship of these receptors to control of acetylcholine output by the nerve terminal has been postulated (14).

The usual approach to the design of muscle relaxants is to attempt to find drugs which are purely cholinergic nicotinic blocking drugs with their actions restricted to the postsynaptic membrane. It should be remembered that the usual clinical tests for the presence and adequate reversal of neuromuscular blockade rely on a fading of response with repetitive stimulation, a nerve terminal effect of the drugs. α-Bungarotoxin, a virtually pure postsynaptic receptor-blocking compound shows no train of four decrement nor fatigue with tetanic nerve stimulation. Thus, with our current tests, determining adequate reversal of a pure postsynaptic blocking drug may be quite difficult.

The primary mode of action of atracurium is that of a nondepolarizing neuromuscular blocking drug whose principal effect is a postsynaptic receptor blockade. Atracurium possesses some nerve terminal inhibitory property as is evidenced by the decreased quantum content of the EPP at 2 and 15 Hz rates of stimulation.

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Selective Kappa Opioid Agonist for Spinal Analgesia without the Risk of Respiratory Depression

Raul Castillo, MD, Igor Kissin, MD, PhD, and Edwin L. Bradley, PhD

CASTILLO R, KISSIN I, BRADLEY EL. Selective kappa opioid agonist for spinal analgesia without the risk of respiratory depression. Anesth Analg 1986;65:350–4.

The effects of the selective κ agonist, U-50,488H, on the motor response to noxious mechanical stimulation when administered intrathecally, as well as on respiratory rate and Pa_{CO_2} *when administered by intracerebroventricular injection, were compared with those of morphine in experiments on rats. The agonist U-50,488H caused a dose-dependent increase in the threshold to noxious stimulation but did not have a potential for depression of resting ventilation. The results suggest that selective κ opioid agonists may be suitable for clinical spinal (epidural) analgesia without the associated risk of respiratory depression.*

Key Words: ANESTHETIC TECHNIQUES—spinal. ANALGESICS—opioid.

The treatment of pain with spinal and epidural administration of morphine has offered a new approach for pain management (1,2). The most significant side effect after this type of opioid administration is a potentially life-threatening respiratory depression (3). The delayed nature of the depression makes it especially dangerous. Therefore, despite the very low incidence of this side effect, physicians are reluctant to use spinal (epidural) opioids for pain relief. It has been suggested that opioid-induced analgesia and respiratory depression are mediated through different subtypes of opioid receptors (4–6). Appearance of opioid agonists selective for certain subtypes of receptors suggests, therefore, that it may be possible to find an opioid that will provide spinal analgesia without risk of respiratory depression in case of supraspinal redistribution of the agent. Kappa opioid agonists are especially interesting in this regard. The κ receptor profile was originally described by Martin et al. (7). They demonstrated the analgesic effect of κ opioid agonist (EKS) in the spinally transected dog. Schmauss and Yaksh (8) have suggested that there are three distinct populations of opioid receptors in the spinal cord, the activation of which results in a selective modulation of the response of the animals to noxious stimuli. In rats with chronically implanted intrathecal catheters, they demonstrated that responses to cutaneous thermal stimulation were modulated by μ and δ receptors, whereas responses to visceral chemical stimulation were modulated by μ and κ receptors. As far as opioid-induced respiratory depression is concerned, two subtypes of opioid receptors are under consideration for mediation of this effect: δ and μ-2 (5,9–11).

The purpose of this study was to find out whether a κ opioid agonist can provide spinal analgesia with somatic mechanical stimulation and be free from the potential for respiratory depression. The agonist U-50,488H (12,13) was used as a selective κ agonist. It is a structurally novel opioid (12,13)—(trans-)(dl)-3, 4-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-(benzeneacetamide) methane sulfonate hydrate. In comparison with the reputed κ opioid agonists, ketazocine and ethylketocyclazocine, U-50,488H was shown to be a more selective κ agonist.

Methods

Sixty-two male Sprague-Dawley rats (300–350 g) with chronically implanted lumbar or cerebral ventricular catheters were used for the study. Lumbar intrathecal catheters (PE-10) were implanted according to the method of Yaksh and Rudy (14). Cerebral ventricular catheters (PE-20) were implanted in the left lateral cerebral ventricle according to the method of Brakkee et al. (15). The position of the catheter was verified after the experiment by the injection of india ink. Surgical procedures for implantation of the catheters

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Address correspondence to Dr. Kissin, Department of Anesthesiology, University of Alabama at Birmingham, University Station Birmingham, AL 35294.

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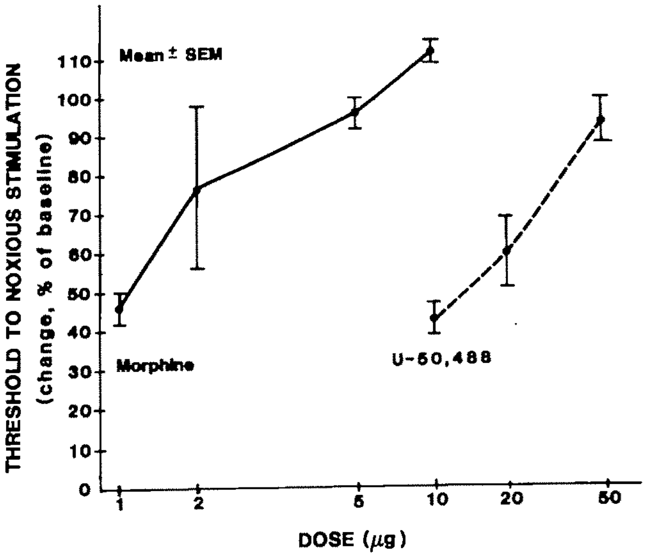

Figure 1. Effect of intrathecal U-50,488H and morphine sulfate on motor reaction threshold to noxious stimulation. Ordinate, change in the reaction threshold; abscissa, dose on a logarithmic scale. Each point represents the mean ± SEM of determinations made in a separate group of four rats.

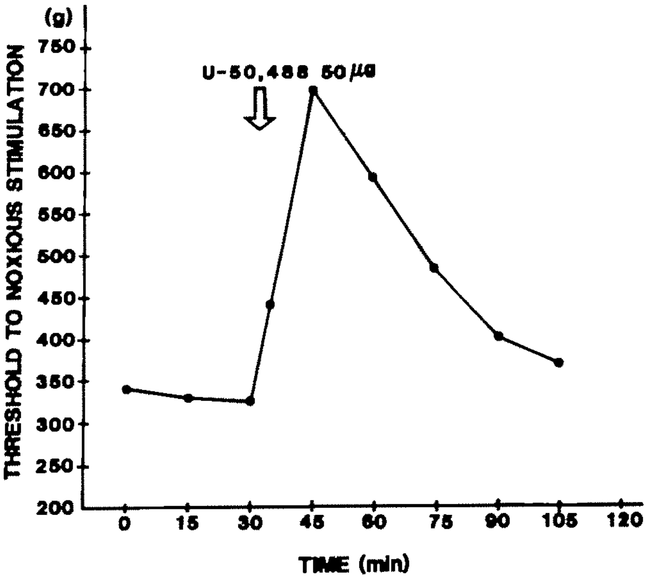

Figure 2. An example of time course of the effect of intrathecal U-50,488H (50 μg) on the reaction threshold to noxious stimulation.

were performed with the rats under pentobarbital anesthesia (50 mg/kg, intraperitoneally) 4 or 5 days before the experiments.

For nociceptive testing, we used the motor responses to increasing pressure on the tail (16). Reaction threshold was determined with the use of an Analgesy-meter (Ugobasile, Milan, Italy). Each rat's tail was positioned on a Teflon platform, and the pressure plate (0.7 mm edge) attached to the device was placed 1–2 cm from the tip of the tail (the rat was held by the experimenter's hand). Pressure was increased at the constant rate of 80 g/sec until the animal made an attempt to escape (coordinated struggle). The pressure at that moment was recorded, and the mean of three consecutive measurements was taken as the reaction threshold. The threshold was measured every 15 min, three or four times before administration of an agent, and four–six times after (depending on the duration of the effect).

Respiratory depression was measured by the change in the respiratory rate. Respiratory movements were recorded with the technique similar to that described by Hunt and Kimeldorf (17). A thin rubber belt was placed around the chest and connected to a force displacement transducer (Grass FTO3). The rats were sitting in a plastic restrainer (Harvard Universal Rat Restrainer), and the rubber belt was connected to the transducer with a thread passing through a slot in the restrainer. The output from the transducer was displayed on a polygraph (Grass D7). The respiratory rate was recorded for about 45 min before the agent was injected.

In a separate series of experiments, respiratory depression was studied by measuring changes in Pa_{CO_2}. The rats used in this series of experiments were surgically prepared to have the catheter (PE-10) in the aorta (placed through the femoral artery). The peripheral end of the catheter was tunneled subcutaneously and exteriorized at the back of the neck. The catheter was kept patent with heparinized saline (100 U/ml). The cannula was placed simultaneously with the implantation of a cerebroventricular catheter. On the day of the experiment, each rat was placed in the restrainer 30 min before the experiment. After this period blood samples (0.2 ml) were withdrawn from the catheter before, and every 10–15 min after opioid administration for a total of five samples. Immediately before the investigator took a sample, 0.15 ml of blood was withdrawn from the catheter to prevent 0.1 ml dead space from affecting the Pa_{CO_2} measurement (the 0.15 ml volume was injected back after the sample was taken). Arterial blood gas tensions were measured using an IL System 1303 Blood Gas Analyzer (Instrumentation Laboratory, Inc.).

The following series of experiments were performed: analgesia series with spinal administration of agents and two respiratory depression series with intracerebroventricular injections of opioids. In each series of experiments, there was a subseries of experiments performed with U-50,488H and with a reference

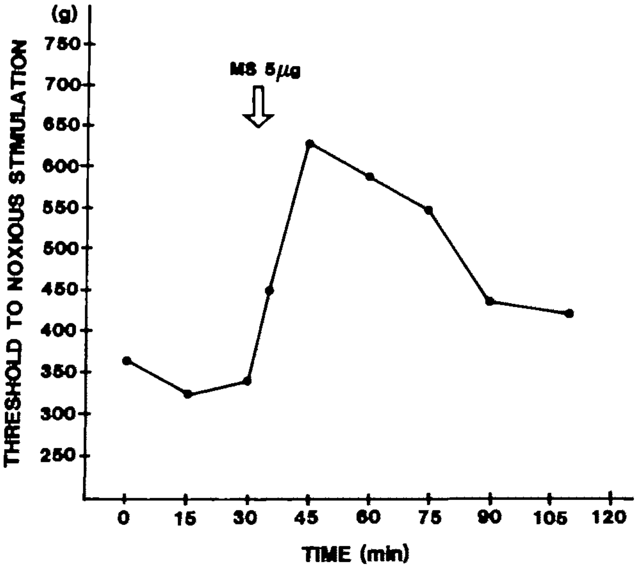

Figure 3. An example of time course of the effect of intrathecal morphine sulfate (5 μg) on the reaction threshold to noxious stimulation.

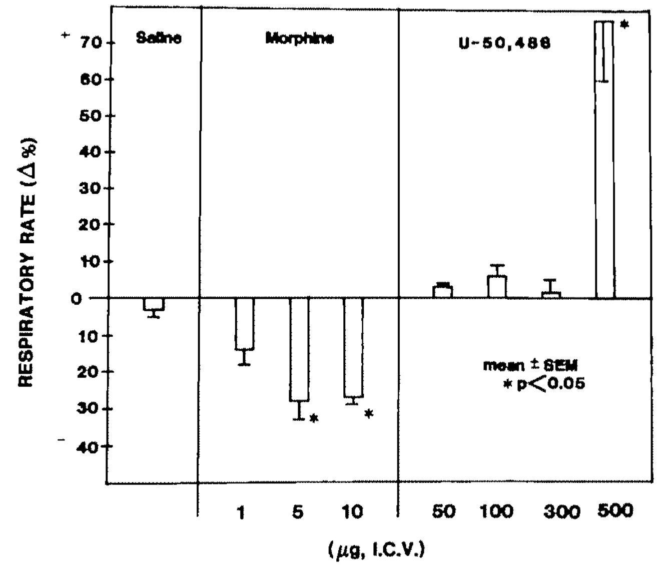

Figure 4. Effect of intracerebroventricular U-50,488H and morphine on respiratory rate.

agent, morphine sulfate. In the analgesia series, morphine was used in doses 1, 2, 5, and 10 μg (four animals for every dose) and U-50,488H in doses of 10, 20, and 50 μg (also four animals for every dose). In the respiratory rate series, morphine was used in doses of 1, 5, and 10 μg (four animals per dose) and U-50,488H in doses of 50, 100, 300, and 500 μg with three animals per dose. A control group of four animals was also used that received an injection of 10 μl of Elliot's B solution. In the Pa_{CO_2} series, morphine was used in a dose of 10 μg and U-50,488H in a dose of 300 μg (six animals). In all experiments, each animal was given only one dose of an agent.

All values are summarized as the mean plus or minus the standard error of the mean. Percentage changes in the respiratory rates were analyzed by a one-way analysis of variance and one-sample *t*-tests. The differences in Pa_{CO_2} changes were assessed by a repeated measures analysis of variance (18). A linear regression model relating motor reaction threshold to drug doses on a logarithmic scale was fit by the method of least squares. These equations were used to estimate the dose of each drug that corresponded to a 50% increase in the threshold value and their associated potency ratio (19). Results were statistically significant at $P < 0.05$.

Drugs were injected with a Hamilton syringe. They were dissolved in Elliot's B solution (NaCl, 126 mM; $NaHCO_3$, 23 mM; Na_2HPO_4, 3 mM; $MgSO_4$, 1 mM; KCl, 4 mM; glucose, 4 mM). Volume of injection was from 10 to 15 μl. Morphine sulfate was obtained from the Merck Company; U-50,488H was a gift from the Upjohn Company.

Results

Figure 1 shows U-50,488H and morphine dose–effect curves for motor reaction threshold to noxious stimulation of the tail. As can be seen, U-50,488H produced a dose-dependent increase in the reaction threshold after intrathecal injection. The dose of U-50,488H that increased reaction threshold by 50% was 13.2 μg. The analogous dose of morphine was 0.96 μg. Considering this level of the response, the intrathecal potency of U-50,488H was approximately 1/13 the potency of morphine. Figures 2 and 3 present examples of the time courses of the effects of U-50,488H (50 μg) and morphine (5 μg) on the reaction threshold.

Effects of U-50,488H and morphine on respiratory rate are shown in Figure 4. As compared with the control group (saline), morphine significantly decreased the respiratory rate after intracerebroventricular administration in doses of 5 and 10 μg. At the same time, U-50,488H in the dose range from 50 to 300 μg did not change the respiratory rate. Further increase in the dose, up to 500 μg, caused excitation with an increase in respiratory rate by approximately 75%.

Pa_{CO_2} measurement yielded a mean baseline value of 41 ± 2 mm Hg. Administration of morphine (10 μg, intracerebroventricularly) significantly increased Pa_{CO_2} (Fig. 6). At the same time, injection of U-50,488H

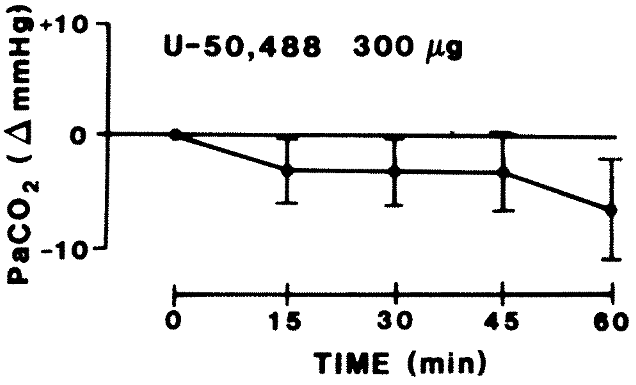

Figure 5. The effect of the intracerebroventricular injection of U-50,488H (300 μg) on Pa_{CO_2}.

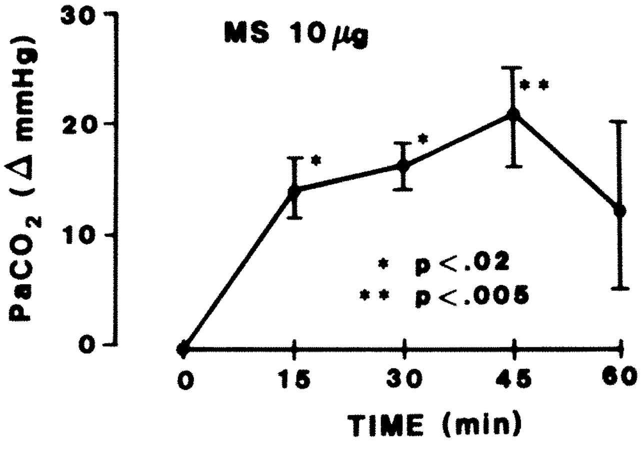

Figure 6. The effect of the intracerebroventricular injection of morphine sulfate (10 μg) on Pa_{CO_2}.

(300 μg, intracerebroventricularly) did not induce any increase in Pa_{CO_2}. On the contrary there was a tendency for Pa_{CO_2} to decrease (Fig. 5).

Discussion

Studies of the benzomorphan analogs (7) and endorphines (20) have led to the hypothesis that separate subclasses of opioid receptors exist. These subclasses may mediate difference pharmacologic effects. With the appearance of opioid agonists selective for a certain subclass of opioid receptors, the possibility is now being investigated that some of the selective agonists may prove to be useful analgesics without many of the undesirable effects of morphine. In the present study we tested a hypothesis that a κ opioid agonist may provide pronounced spinal analgesia for somatic mechanical stimulations without respiratory depression. There are a number of reputed κ opioid agonists, such as ketazocine, ethylketocyclazocine, and bremazocine. For our study, we used U-50,488H, which is a more selective κ agonist (21). It was discovered by Szmuszkovicz and VonVoigtlander (Upjohn Co.) and currently is in use as an experimental compound (12,13).

In our experiments, the κ opioid agonist U-50,488H, in contrast to morphine, did not cause respiratory depression in rats. When U-50,488H was used in the dose range from 50 to 300 μg, no decrease in respiratory rate was found (and some increase with 500 μg). Measurement of Pa_{CO_2} confirmed absence of any significant depression of resting ventilation with U-50,488H, 300 μg, intracerebroventricularly (but this does not necessarily prove that the slope of the ventilatory response to increased carbon dioxide tensions is equally unaffected). Our data agree with the concept that opioid-induced respiratory depression is mediated by μ-2, or delta receptors, or both (11,22). Because U-50,488H is a selective κ opioid agonist (13,21), it probably does not interact to any significant extent with the subtypes of opioid receptors that mediate respiratory depression.

Along with the absence of respiratory depression with intracerebroventricular administration of U-50,488H, we found that this agent, when used intrathecally, caused a pronounced analgesic effect with the tail pressure test. U-50,488H demonstrated about 1/13 the potency of morphine with this test. Yaksh and Schmauss found that U-50,488H administered intrathecally had approximately 1/10 the potency of morphine when visceral nociceptive stimulation was used (writhing response) (8). It should be noted that with thermal stimulation (tail flick response), U-50,488H was only marginally active in rats (8). This agrees with the observations regarding another κ agonist—EKC—which, when used intrathecally, has little effect in suppressing the thermally evoked reflexes (7,23). Tyers first suggested that different opioid receptors mediate antinociceptive actions against different types of noxious stimuli (24). Yaksh et al. clearly demonstrated this on the spinal level (8,23). If a unique association between the particular receptor and a given neural substrate that mediates the spinal processing of a specific class of stimulus exists, selective opioid agonists may not be helpful with every type of pain. Kappa opioid agonists probably are effective against somatic pain caused by mechanical stimulation and visceral pain caused by chemical stimulation, but not against cutaneous pain caused by thermal stimulation. The involvement of κ receptors in useful analgesia for different types of pain in humans remains to be established.

The present data suggest that selective κ opioid agonists may potentially be able to provide clinical spinal (or epidural) analgesia without risk of respiratory depression. In addition, the data may offer a new way to deal with the development of tolerance to the narcotic analgesics. The development of tolerance is one of the most important complications of spinal (epidural) analgesia with narcotics (25). Lack of cross-tolerance between agents acting on different opioid receptors is well-known (3); mice treated chronically with U-50,488H do not, for example, develop cross-tolerance to morphine (12). Therefore if tolerance to a selective κ opioid agonist develops, it might be expected that morphine, acting through other subtypes of opioid receptors, may be used as a reserve agent for spinal analgesia. It should be kept in mind that the absence of respiratory depression with the use of selective κ opioids in the rat does not necessarily imply the same effect in humans.

In conclusion, rat experiments demonstrate that U-50,488H causes a dose-dependent increase in the threshold to noxious mechanical stimulation and, at the same time, does not have a potential for depression of resting ventilation.

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The Effects of Nitrous Oxide on Oxygen Consumption by Isolated Cerebral Cortex Mitochondria

Gerald L. Becker, MD, Dale A. Pelligrino, PhD, David J. Miletich, PhD, and Ronald F. Albrecht, MD

BECKER GL, PELLIGRINO DA, MILETICH DJ, ALBRECHT RF. The effects of nitrous oxide on oxygen consumption by isolated cerebral cortex mitochondria. Anesth Analg 1986;65:355–9.

The influence of N_2O on O_2 consumption by mitochondria isolated from the cerebral cortex of goats was examined in incubations preequilibrated with N_2O–O_2 or N_2–O_2. Rates of O_2 consumption were measured polarographically in a closed system while adenosine triphosphate (ATP) formation was maximal (after addition of excess adenosine diphosphate (ADP), state 3 respiration) and then when it was at zero (after addition of excess oligomycin, state 4 respiration). Compared with 90% N_2, 90% N_2O produced no change in the rate of state 3 respiration; but an observed 9% decrease in the state 4 rate and an 11% increase in the state 3:state 4 ratio were statistically significant ($P < 0.05$). These differences were not seen with N_2 and N_2O at 70% rather than at 90%, or when succinate rather than pyruvate–malate was used as the respiratory substrate. We conclude the following: Unlike other inhalation anesthetics, N_2O at comparable anesthetic concentrations does not inhibit mitochondrial electron transport or ATP formation coupled to it (oxidative phosphorylation). N_2O does inhibit one or more other processes, as yet unidentified, which are energetically coupled to electron transport. The increased cerebral O_2 consumption that accompanies N_2O anesthesia cannot be attributed to a direct effect of N_2O on mitochondrial respiration.

Key Words: ANESTHETICS, GASES—nitrous oxide. METABOLISM—oxygen consumption. OXYGEN, CONSUMPTION—brain.

Although more widely used, N_2O is less well understood in its actions than are other inhalation anesthetics. The latter have been found as a group to inhibit adenosine diphosphate (ADP)-stimulated mitochondrial O_2 consumption (state 3 respiration) in vitro, with individual potencies that correlate well with the respective anesthetic potencies (1). This correlation had not been established for N_2O: inhibition of state 3 respiration by N_2O in liver mitochondria was demonstrated only when halothane was also present (2). We have therefore investigated whether N_2O at physiologically relevant concentrations and in the absence of other anesthetics has direct effects on state 3 and state 4 (ADP-independent) respiration in cerebral cortex mitochondria.

Methods

Adult male goats were anesthetized with enflurane, then intubated and ventilated while brains were rapidly removed. The total time required for anesthesia and brain removal was always less than 10 min. Brains were cooled by immersion in ice-cold isolation medium consisting of 0.32 M sucrose, 1 mM ethylene glycol bis(B-aminoethyl ether)-N,N,N′,N′-tetraacetic acid (EGTA), 5 mM 4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid (HEPES), and 0.1% bovine serum albumin, all adjusted to pH 7.2 with KOH. From the 7–8 g of cortex obtained by dissection, a mitochondrial fraction was isolated using an adaptation of published procedures (3–5). Specifically, whole tissue was thoroughly minced, diluted 5-fold with isolation medium, and homogenized with 4 up-and-down strokes in a Potter–Elvejhem homogenizer. Nuclei and undisrupted cells were removed by sedimentation at 600 g for 10 min; the remaining supernatant was then centrifuged at 14,000 g for 10 min to pellet the crude mitochondrial fraction. The mitochondrial pellet was resuspended in a minimum volume of fresh medium and layered onto a 20-ml "cushion" of 0.32 M sucrose

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Address correspondence to Dr. Becker, Department of Anesthesiology, Michael Reese Hospital, 31st Street and Lake Shore Drive, Chicago, IL 60616.

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Table 1.. Cerebral Mitochondrial Respiratory Parameters: Absolute Values

Substrate	Gas phase	State 3 rate (nmol·min^{-1}·mg^{1})	State 4 rate (nmol·min^{-1}·mg^{-1})	Respiratory control ratio
Pyruvate (n = 17)	N_2O–O_2	21.8 ± 1.8	2.7 ± 0.2[a]	8.2 ± 0.6[a]
	N_2–O_2	21.3 ± 1.8	3.0 ± 0.3	7.4 ± 0.5
Succinate (n = 15)	N_2O–O_2	18.6 ± 2.1	5.4 ± 0.5	3.4 ± 0.2
	N_2–O_2	19.2 ± 3.0	5.3 ± 0.6	3.5 ± 0.3

Values shown are mean ± SEM.

[a] $P < 0.05$ for N_2O–O_2 vs N_2–O_2.

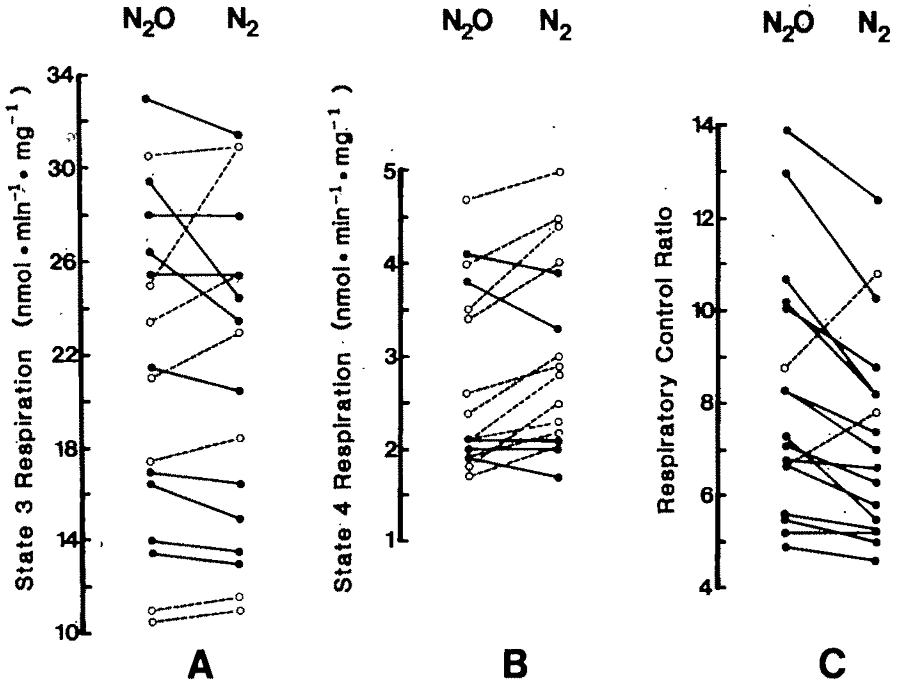

Figure 1. Individual values of respiratory parameters in isolated cerebral cortex mitochondria incubated with pyruvate–malate as substrate and equilibrated with 90% N_2O or N_2. (A) State 3 respiration. (B) State 4 respiration. (C) Respiratory control ratio. Lines connect values obtained from the same mitochondrial preparation: open circles and dotted lines, N_2 value > N_2O value; closed circles and solid lines, N_2 value < N_2O value. All data were obtained from the same set of 17 different mitochondrial preparations; (B) contains only 16 separate lines because two preparations showed identical values with both N_2O and N_2.

containing 4% w/v Ficoll (Sigma Chemical Company). Subsequent centrifugation at 40,000 g for 30 min sedimented mitochondria while leaving in suspension contaminating membranes, especially those of synaptosomes. Mitochondria were resuspended to a final protein concentration of 40–80 mg/ml, as determined by the procedure of Bradford (6).

Oxygen consumption was measured polarographically at 37°C using a membrane-covered Clark electrode fitted into a 2-ml incubation chamber (Gilson Medical Electronics, Middleton, WI). The medium contained 120 mM KCl, 25 mM HEPES, 4 mM $MgCl_2$, 3 mM ATP, 2 mM PO_4, and either 5 mM pyruvate/5 mM malate or 5 mM succinate, at pH 7.0. N_2O or N_2 mixed with O_2 (10% or 30%) was bubbled into this medium at 400 ml/min for at least 5 min through a needle attached to the outflow line of an anesthesia machine. In rapid succession the needle was withdrawn, the chamber stoppered, and the mitochondrial suspension (4 mg protein) added through an injection port to completely fill the chamber and initiate O_2 consumption. After 10–15 sec of further equilibration, sufficient ADP (400 nmol) was added to stimulate the maximum rate of coupled respiration (state 3 as defined by Chance and Williams (7)). As has previously been reported by others (4), state 4 (ADP-unstimulated) respiration was not spontaneously attained in incubation medium containing Mg^{2+}. Therefore, after ADP had been added and the ensuing linear state 3 rate measured for 1–2 min, the equivalent of state 4 was imposed by adding oligomycin (5 μg) to inhibit mitochondrial adenosine triphosphate (ATP) synthetase (4). After measuring state 4 for another 1–2 min, the respiratory control ratio (RCR) was calculated as the state 3 (ADP-stimulated) rate divided by the state 4 (oligomycin-inhibited) rate.

Values of respiratory parameters measured in isolated mitochondria can show considerable between-experiment variation due to uncontrollable differences in the mitochondrial preparations themselves. Because this variation can be large enough to obscure effects arising from manipulation of the experimental variables, differences between N_2O and N_2 exposure were assessed by pairing and comparing values obtained from the same mitochondrial preparation, then using the *t*-test to determine whether those differences as a group differed significantly from zero [the paired *t*-test (8)]. $P < 0.05$ was considered statistically significant.

Results

Table 1 presents average values of mitochondrial respiratory parameters obtained from incubations equilibrated with 90% N_2 or N_2O. Absolute values for state 3 and state 4 rates and RCRs agree well with those reported by other laboratories for isolated brain mitochondria (4,5). Also evident are the higher state 4 rates and lower RCRs when succinate, rather than pyruvate–malate, is used as substrate, as first reported by Clark and Nicklas (3).

Figure 1 shows individual values of all three respiratory parameters obtained with the 17 different mitochondrial preparations incubated with pyruvate–malate as substrate and exposed to either 90% N_2O or N_2. For each parameter there was considerable overlap among groups of values obtained with N_2O and N_2. However, when values from the same preparation (those joined by lines in Fig. 1) were compared, 13 of 17 RCRs (Fig. 1C) obtained with N_2O were higher than corresponding values with N_2, a statistically significant ($P < 0.05$) preponderance by paired *t*-test. Similarly, state 4 values with N_2O were, as a group, significantly lower than their N_2 counterparts; whereas state 3 values showed no dependence on composition of the gas phase. Furthermore, no N_2O-associated change in any respiratory parameter was seen with succinate as substrate (Table 1), or with N_2O and N_2 at 70% rather than 90% (data not shown).

Table 2 shows the same results as Table 1 but with N_2O values expressed as fractions of the N_2 values so that differences may be more easily judged. Compared with N_2, N_2O produced no change in state 3, a 9% decrease in state 4, and an 11% increase in RCR.

Discussion

The major findings and conclusions of this study derive from the pattern of observed N_2O effects on respiratory states of isolated cerebral cortex mitochondria.

Nitrous oxide did not alter state 3 respiration. This finding sets N_2O apart from other anesthetics: those with reported mitochondrial effects inhibited state 3 respiration in vitro, when tested at concentrations equianesthetic with 70–90% N_2O (9). Specifically, state 3 respiration in isolated rat liver mitochondria was decreased by about 20% in the presence of 0.4% halothane (~ 0.5 MAC) (10) and by about 15% with 0.6% enflurane (~ 0.4 MAC) (11). Assuming (conservatively) that 90% N_2O represented the equivalent of only 0.5 MAC, a decrease in state 3 respiration of 15–20% from the value obtained with control (90% N_2) would have been expected in this study, had the effect of N_2O been comparable to that of the other inhalation anesthetics. Lack of state 3 inhibition means that N_2O did not interfere with mitochondrial oxidative phosphorylation (ATP production) even at the latter's maximal rate. Furthermore, because electron flow along the respiratory chain is near-maximal in state 3, such inhibition would have been detected with considerable sensitivity.

Table 2. Cerebral Mitochondrial Respiratory Parameters: $\frac{N_2O \text{ value}}{N_2 \text{ value}}$

Substrate	State 3 rate	State 4 rate	Respiratory control ratio
Pyruvate (*n* = 17)	1.00 ± 0.02	0.91 ± 0.05[a]	1.11 ± 0.03[a]
Succinate (*n* = 15)	1.02 ± 0.05	1.06 ± 0.07	1.00 ± 0.05

Values shown are mean ± SEM.
[a] $P < 0.05$ for $N_2O–O_2$ vs $N_2–O_2$.

Nitrous oxide inhibited state 4 respiration. In this respect, too, N_2O differed from other anesthetics, which were reported to produce negligible effects on state 4 respiration at doses that substantially inhibited state 3 (1). In addition, our finding that N_2O inhibited state 4 confirmed that 90% N_2O was a sufficiently high concentration to elicit effects on mitochondrial respiration. The lack of observed state 3 inhibition with 90% N_2O in this study can therefore be ascribed to the actual absence of that particular effect and not merely to the use of an N_2O concentration too low to produce a detectable response.

Nitrous oxide did not increase state 4 rates. This result rules out an uncoupler-like action of N_2O that might have explained our laboratory's earlier finding that N_2O anesthesia in goats increased cerebral metabolic rates without changes in tissue high-energy phosphates (12). We now favor the alternative explanation that shifts in phosphorylation state sufficient to stimulate O_2 consumption did occur but were not detected by the analytical procedures used, a common technical problem in assessment of energy status from samples of intact tissue (13).

In the present study, the use of fractionally higher N_2O and N_2 concentrations (90%) was crucial to eliciting a differential response because none was discernible at 70%, in agreement with Nahrwold and Cohen's results with liver mitochondria (2). The concomitant use of O_2 at 10% probably improved the simulation of in vivo conditions, because intracellular O_2 tensions in the vicinity of mitochondria are thought to be at least that low in metabolically active tissues (14,15). On the other hand, the use of hyperbaric techniques to achieve still higher concentrations of dissolved N_2O, and thus encompass a larger portion of the N_2O dose–response curve, would have added another variable and been inconsistent with the aim of simulating clinically relevant conditions in vitro.

Concentrations of N_2O, N_2, and O_2 dissolved in the incubation medium after gassing were not measured directly, raising the possibility that the observed effects were due to systematic differences in P_{O_2} between N_2O–O_2 and N_2–O_2 incubations, arising from discrepancies in absolute rates of N_2O and N_2 delivery by the anesthesia machine. However, the rates of both state 3 and state 4 respiration have previously been shown to be independent of P_{O_2} for values ranging from 1 atm to less than 1 mm Hg (16) for a variety of mitochondrial preparations.

The possibility that enflurane administered during brain removal may have altered the response of isolated mitochondria to subsequent N_2O exposure cannot be excluded based on the data in this study. However, the probability of such an effect is mitigated by the relatively short duration of enflurane exposure (10 min) compared to the ensuing 2- to 3-h preparation period over which tissue fractions equilibrated freely with room air. The likely dissipation of enflurane within that interval is supported by the finding that halothane-induced alterations of mitochondrial respiration were absent if halothane exposure was limited to brief anesthesia prior to mitochondrial isolation (17).

The data reported here do not support the conclusion of Nahrwold and Cohen (2) that N_2O is capable of inhibiting state 3 respiration in mitochondria. These investigators found no inhibition of state 3 by 70% N_2O alone, whereas 70% N_2O mixed with a calculated equipotent dose of halothane produced inhibition exceeding that expected from halothane alone. However, the contribution of halothane to the total observed inhibition appears to have been underestimated because the authors used an interpolated value of ID_{50} considerably higher than a directly measured value from their own laboratory (18). Thus inhibition attributed to N_2O was actually produced by halothane. Their study reported no measurements of state 4 rates; therefore no comparison can be made with the effects noted by us.

The significance of N_2O-mediated effects on mitochondrial respiration lies less in their magnitude than in their implication for understanding the mechanisms of N_2O action. Nahrwold and Cohen (2) found that N_2O showed the same relationship between state 3 inhibition and anesthetic potency demonstrated by other general anesthetics (9), which supports their proposed theory of unitary mechanism of anesthetic interactions with mitochondrial membrane-localized reactions (18). By the same reasoning, we feel that our equally well-documented but different pattern of mitochondrial effects raises doubts about the uniformity of such interactions.

The finding of N_2O-mediated effects on mitochondrial state 4 respiration, like previously reported state 3 effects of other anesthetics (9), can be further examined to ascertain which component reaction(s) may have been affected by N_2O. Nitrous oxide action on the respiratory chain or ADP phosphorylation can be excluded because state 3 effects were absent, as discussed earlier. In state 4, energy release is coupled not to ATP formation but rather to continuous active transport of H^+ and Ca^{2+} that maintains steady-state electrochemical gradients of these ions across the mitochondrial membrane (19). Inhibition of Ca^{2+} transport by N_2O could not have accounted for decreased state 4 O_2 consumption, because abolishing Ca^{2+} transport by adding EGTA to chelate available Ca^{2+} (20) did not eliminate the differences between N_2O and N_2 effects on state 4 respiratory rates (unpublished observations). The alternative possibility that N_2O produced decreases in H^+ transport is strengthened by the known sensitivity of transmembrane H^+ fluxes to changes in membrane permeability (19). The latter is in turn governed by physicochemical properties such as fluidity known to be altered by anesthetics (21).

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Norepinephrine Uptake in Canine Saphenous Veins in the Presence and Absence of Halothane

Larry W. Hunter, MS, Duane K. Rorie, MD, PhD, and Gertrude M. Tyce, PhD

HUNTER LW, RORIE DK, TYCE GM. Norepinephrine uptake in canine saphenous veins in the presence and absence of halothane. Anesth Analg 1986;65:360–4.

Studies were done to examine neuronal and extraneuronal uptakes of norepinephrine in canine saphenous veins and to ascertain whether these uptakes were altered by halothane. Minced vein was incubated for 1 min in Krebs–Ringer solution containing L-[ring-2,5,6-^{3}H]–norepinephrine (1, 2.5, 6, or 12 μM). After incubation, radioactivity in tissue was measured by liquid scintillation counting. Neuronal uptake at each norepinephrine concentration was determined by the difference in norepinephrine uptake between tissues in which both neuronal and extraneuronal uptakes were operative and in tissues in which only extraneuronal uptake was operative. In time studies with 1 μM norepinephrine, neuronal uptake was still dominant at 10 min; with 12 μM norepinephrine, extraneuronal uptake predominated at all incubation periods tested. In other studies, tissues were incubated in the absence or presence of halothane (2.5%). The K_m values for neuronal uptake in control and halothane-treated tissues were 2.49 and 2.32 μM, respectively. Corresponding V_{max} values were 0.049 and 0.060 nMol·min^{-1}·100 mg^{-1}, respectively. No significant effect of halothane on neuronal or extraneuronal uptake could be detected.

Key Words: ANESTHETICS, VOLATILE—halothane. SYMPATHETIC NERVOUS SYSTEM—neuronal norepinephrine uptake.

At synaptic clefts in blood vessels the amount of neurotransmitter norepinephrine (NE) available to interact with postsynaptic receptors is dependent upon the balance between the amount of NE released and the amounts of NE removed by neuronal uptake, extraneuronal uptake, and overflow from the cleft (1–4). Historically neuronal uptake was considered to be the most important for removal of released NE because this uptake was reported to have a high affinity for NE (5). By contrast, extraneuronal uptake, with its low affinity but high capacity, was presumed to become active only when neuronal uptake was overwhelmed (6). More recent studies question this concept and have suggested that extraneuronal uptake participates in removing NE from the cleft even at low concentrations of NE (4,7,8).

A decrease in removal of NE from the synaptic cleft by either neuronal or extraneuronal uptake or an increase in release of NE from the nerve endings could be expected to increase the NE concentration in the synaptic cleft, thereby increasing the overflow of NE from the cleft into the circulation. Evidence that halothane may inhibit neuronal (9) and extraneuronal (10) uptakes has been presented, although this hypothesis has not been supported by all studies (11–13). The present studies were undertaken to examine neuronal and extraneuronal uptakes of NE in canine saphenous veins and to determine whether halothane altered these processes. K_m and V_{max} values for neuronal uptake were determined in control and halothane-treated veins.

Methods

Experimental Design

A time study was first performed to ascertain the incubation period during which the initial rate of neuronal uptake was linear. Studies were performed with a relatively low (1 μM) and a relatively high (12 μM) concentration of [^{3}H]NE. After an appropriate incubation time was determined in the time study, a study involving incubation of each tissue for a fixed time (1 min) with a range of [^{3}H]NE concentrations (1, 2.5, 6, or 12 μM) was undertaken to yield the uptake saturation curve necessary to determine the K_m and V_{max} values for neuronal uptake (14). For the saturation study, tissues were incubated in two sets: one set was

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Address correspondence to Dr. Rorie, Department of Anesthesiology, Mayo Clinic, Rochester, MN 55905.

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incubated in the presence, and the other in the absence of 2.5% halothane.

Vein Collection and Preparation

Adult mongrel dogs (20–30 kg) of either sex were fasted for 1 day before being anesthetized with pentobarbital sodium (30 mg·kg^{-1}, intravenously). A lateral saphenous vein was removed and placed in preoxygenated Krebs–Ringer solution (4). Each vein was cleaned of surrounding fascia and cut longitudinally to yield a flat strip. Each strip was then minced with scissors into pieces approximately 1 mm on a side. The mince was rinsed in fresh Krebs–Ringer solution. The tubes containing the tissue samples were then placed in a water bath at 37°C, bubbled with 5% CO_2 in oxygen and allowed to undergo posthandling stabilization. After 100 min, the volume of Krebs–Ringer solution in each tube was reduced to 2 ml, and the incubation and aeration were continued for an additional 30 min.

Determination of Neuronal Uptake With Time

After the second incubation phase, an additional 2 ml of Krebs–Ringer solution was added to each sample. The solution contained sufficient amounts of the following compounds to give a final concentration of: either 0.09 or 0.18 μCi·ml^{-1} of ^{3}H-(−) norepinephrine ([^{3}H]NE); either 1, 2.5, 6, or 12 μM unlabeled (−) norepinephrine; 0.05 μCi·ml^{-1} of ^{14}C-(+) sorbitol; 0.01% EDTA; and 0.01% ascorbic acid. For determination of linearity of neuronal uptake with time, tissues were incubated in duplicate either in 1 μM [^{3}H]NE (0.09 μCi·ml^{-1}) for 1, 2, 5, or 10 min; or in 12 μM [^{3}H]NE (0.18 μCi·ml^{-1}) for 0.75, 1, 1.5, or 2 min. Uptake values of duplicate samples were averaged. Uptake of [^{3}H]NE was terminated by transferring each tissue sample to 5 ml of ice-cold Krebs–Ringer solution for 10 sec. Tissues were then blotted and weighed. The average (± SEM) weight of tissues studied in each experiment was 15.8 ± 0.2 mg (n = 224).

Determination of [^{3}H]NE Uptakes

Neuronal uptake (uptake of [^{3}H]NE into nerve endings), extraneuronal uptake (uptake of [^{3}H]NE into nonneuronal tissues), and total uptake of [^{3}H]NE (neuronal plus extraneuronal uptakes) were measured or derived in each experiment according to the following protocols: All tissues were paired; one sample from each pair had cocaine (100 μM) added during the last 30 min of the tissue stabilization period preceding radioactive labeling, whereas the other sample did not. This concentration of cocaine serves as a potent inhibitor of neuronal amine uptake (15). Total uptake of [^{3}H]NE was determined from the sample not treated with cocaine. Uptake of [^{3}H]NE in the presence of cocaine was taken to be extraneuronal, and was subtracted from total uptake to yield neuronal uptake. The [^{3}H]NE content of tissue neuronal and extraneuronal compartments was expressed as nMol of [^{3}H]NE taken up per 100-mg tissue wet weight.

Corrections were made for the uptake of [^{3}H]NE within tissue extracellular space (the space between cells making up the tissue). The incubation fluid of all tissues studied contained [^{14}C]sorbitol concurrent with the presence of [^{3}H]NE. It was assumed that, as in other tissues (16), [^{3}H]NE and [^{14}C]sorbitol would spread through the extracellular space of saphenous veins at the same rate. Thus for each incubation period the [^{3}H]NE uptake into extracellular space was calculated from the [^{14}C]sorbitol distribution, and was subtracted from uptake of tritium.

Application of Halothane.

When the effects of 2.5% halothane on uptakes were studied, two sets of paired tissues were incubated. One set (controls) was treated as described (see above), except each tissue pair was incubated in 0.09 μCi·ml^{-1} of [^{3}H]NE at one of four different concentrations (1, 2.5, 6, or 12 μM) for 1 min. The other set was treated identically, except tissues were additionally exposed to 2.5% halothane delivered with the bubbling gas. Halothane was supplied during the last 30 min of the stabilization period preceding incubation and during incubation in [^{3}H]NE. Muldoon et al. (17) have reported that after 30 min exposure venous tissue is equilibrated with halothane. The anesthetic was delivered through a copper kettle vaporizer, and its content in the gas aerating the incubation fluid was monitored continuously with an infrared halothane analyzer (Beckman LBII). Before each experiment the analyzer was calibrated with premixed halothane standards of 0.75% and 2.8%.

Measurement of Radioactivity

After weighing, tissues were solubilized overnight at room temperature in 0.75 ml of Soluene-350. A low-chemiluminescence scintillation cocktail (10 ml) was then added to each sample and ^{3}H and ^{14}C content activity were measured simultaneously by liquid scintillation counting (Beckman Model LS9800). Radioactivity was also measured in duplicate aliquots of the fluid in which each tissue was incubated (0.2 ml samples taken at the end of incubation were added to 10

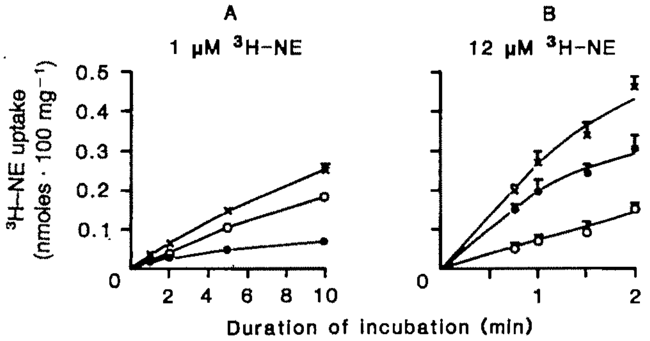

Figure 1. Comparison of the amounts of ^{3}H-(−)norepinephrine ([^{3}H]NE) taken up into canine saphenous vein when [^{3}H]NE concentrations were 1 and 12 μM. Ordinates: Uptake of [^{3}H]NE (nMol·100 mg^{-1} wet weight). Abscissae: Duration of incubation (min) in the presence of 1 μM (A) or 12 μM (B) [^{3}H]NE. Tissues were incubated in 4 ml of 37°C Krebs–Ringer solution containing either 1 μM (0.09 μCi·ml^{-1}) or 12 μM (0.18 μCi·ml^{-1}) [^{3}H]NE. Incubation time varied from 1 to 10 min with 1 μM [^{3}H]NE and from 0.75–2 min with 12 μM [^{3}H]NE. Tissues were always paired; each pair contained one tissue incubated in the presence of cocaine, the other in the absence of cocaine (100 μM). Neuronal uptake (O—O) was determined by the difference in uptake between the cocaine-treated (extraneuronal uptake, ●—●) and the noncocaine-treated tissue (total uptake X—X). [^{14}C]sorbitol (0.5 μCi·ml^{-1}) was used to correct for [^{3}H]NE distribution within tissue extracellular space. Shown are means ± SEM of 4 tissues at each time interval.

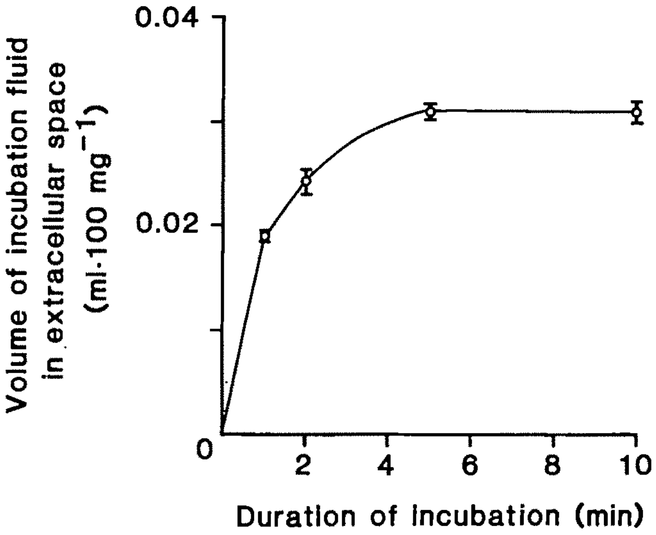

Figure 2. Time-course study of distribution of 1 μM ^{3}H-(−) norepinephrine ([^{3}H]NE) within the extracellular space of canine saphenous vein; 37°C. Ordinate: Uptake of [^{3}H]NE into the extracellular space expressed as ml of incubation medium taken up per 100 mg tissue wet weight. Abscissa: Duration of incubation in min. Tissues were incubated for 1–10 min in 4 ml of Krebs–Ringer solution containing 0.09 μCi·ml^{-1} of [^{3}H]NE and 0.05 μCi·ml^{-1} of [^{14}C]sorbitol. Radioactivity in tissues and in 0.2 ml aliquots of incubation fluid was determined. Shown are means ± SEM; $n = 16$.

ml of high-flashpoint scintillation cocktail). Counting efficiencies for ^{3}H and ^{14}C ranged from 29 to 35% and from 68 to 72%, respectively.

The following materials were used: L-[ring-2,5,6-^{3}H]-norepinephrine (48.4 Ci·mMol^{-1}) (NET 678) and D-[^{14}C(U)]-sorbitol (346.0 mCi·mMol^{-1}) (NEC 386), New England Nuclear, Boston, MA; nonradiolabeled (−) norepinephrine bitartrate salt, Sigma Chemical Company, St. Louis, MO; cocaine hydrochloride, Merck Chemical Division, Rahway, NJ; halothane, Ayerst Incorporated, New York, NY; premixed halothane–oxygen calibrating gas, Ohio Medical Products, Madison, WI; tissue solubilizer (Soluene-350) and low-chemiluminescence scintillation cocktail (Dimilume-30), Packard Company, Downers Grove, IL; high flashpoint scintillation cocktail (Safety-Solve), Research Products International, Mount Prospect, IL.

Results

The Kinetics of Neuronal and Extraneuronal Uptakes in Canine Saphenous Veins

When veins were incubated in 1 μM [^{3}H]NE, uptakes into neuronal and extraneuronal tissues were equal up to 2 min; subsequently neuronal uptake was predominant and remained so throughout the balance of the 10-min incubation (Fig. 1A). During the first 5 min of the incubations, neuronal uptake was linear; between 5 and 10 min of incubation neuronal uptake was not linear and did not fully saturate at 1 μM [^{3}H]NE concentration.

When the incubation fluid contained 12 μM [^{3}H]NE, extraneuronal uptake always predominated (Fig. 1**B**). Neuronal uptake was linear for only 2 min and became saturated by 5 min. Therefore, during time-course studies employing 12 μM [^{3}H]NE, incubation periods were reduced to 0.75, 1.0, 1.5, and 2.0 minutes (Fig. 1**B**).

Uptake into extracellular space proceeded rapidly and was saturated by 5 min (Fig. 2). This uptake was independent of amine concentration. When determined after 10 min of incubation, the extracellular space (i.e., the [^{14}C]sorbitol space) was 0.031 ± 0.001 ml·100 mg^{-1} (mean ± SEM; $n = 16$).

The Effect of Halothane on Neuronal and Extraneuronal Uptakes

The effects of 2.5% halothane on the neuronal and extraneuronal uptakes of [^{3}H]NE were examined in tissues equilibrated with 2.5% halothane or free of halothane. The tissues were incubated for 1 min in concentrations of [^{3}H]NE ranging from 1 μM to 12 μM. The resulting total (Fig. 3A), extraneuronal (Fig. 3**B**), and neuronal (Fig. 3**C**) uptakes are illustrated in Figure 3. Under the conditions described, neu-

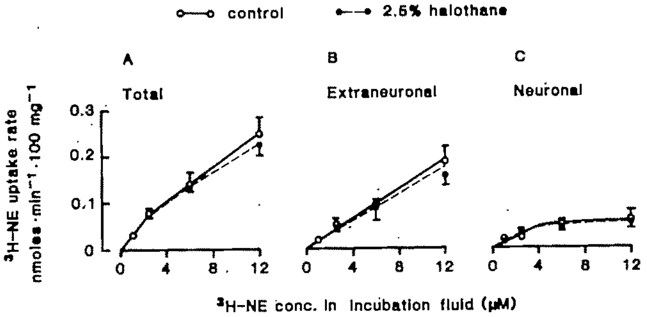

Figure 3. The rate of uptakes of ^{3}H-(−) norepinephrine ([^{3}H]NE) in canine saphenous vein in the presence (●—●) and absence (○—○) of 2.5% halothane; Krebs–Ringer solution, 37°C. Veins were incubated for 1 min in 0.09 μCi·ml^{-1} of [^{3}H]NE (1–12 μM) and 0.05 μCi·ml^{-1} of [^{14}C]sorbitol. Ordinates: Rate of uptake of [^{3}H]NE in nMol·min^{-1}·100 mg^{-1}. Abscissae: Concentration of [^{3}H]NE (μM) in the incubation fluid. Two sets of paired tissues were incubated. One set was aerated with 95% O_2–5% CO_2; the other set was treated identically, except 2.5% halothane was added to the O_2–CO_2 aerating gas. Each tissue pair contained one tissue incubated in the presence of cocaine (100 μM) and another incubated in the absence of cocaine. [^{3}H]NE uptake in tissues not treated with cocaine was considered to be total uptake because both the neuronal and extraneuronal uptake processes were operative. [^{3}H]NE uptake in tissues with neuronal uptake blocked by cocaine was considered to be extraneuronal uptake. Neuronal uptake was calculated from the difference between total and extraneuronal uptakes. Correction was made for the extracellular distribution of [^{3}H]NE (nonneuronal-nonextraneuronal uptake). Values are means ± SEM, $n = 6$.

ronal uptake was saturable and was found to obey the Michaelis–Menten equation when subjected to kinetic analysis. Lineweaver–Burk analysis of neuronal uptake yielded K_m values of 2.49 ± 0.56 μM and 2.32 ± 2.23 μM for control and halothane-treated tissues, respectively (mean ± SEM; $n = 6$ each). Corresponding V_{max} values were 0.049 ± 0.008 nMol·min^{-1}·100 mg^{-1} and 0.060 ± 0.023 nMol·min^{-1}·100 mg^{-1}. Experimental values were not significantly different from controls. The slopes of the double-reciprocal plots were determined by the least-squares method.

Extraneuronal uptake was linear within the range of concentrations studied, and was not significantly affected by halothane (Fig. 3B).

Discussion

The data provide insight into the importance of neuronal and extraneuronal uptakes of NE in the clearance of NE from synaptic clefts in canine saphenous veins. In contrast to earlier observations (5), both extraneuronal and neuronal uptakes are operative at the low concentrations of NE contained in the incubation media. Neuronal uptake did, however, predominate at the lower NE concentration. Moreover, the data relating to neuronal uptake are consistent with a system that is easily saturated; several earlier studies support this finding (18,19). The data also suggest that under the conditions of these experiments, neuronal uptake becomes saturated at a NE concentration between 4 and 6 μM. Extraneuronal uptake appears to have a greater capacity to remove NE from the synaptic cleft than does neuronal uptake, and at higher concentrations of NE in the synaptic cleft, extraneuronal uptake becomes the dominant process for removing NE. Extraneuronal uptake never became saturated at the concentrations of NE used in this study. The greater capacity of extraneuronal uptake may relate to the apparent greater surface area of all nonneuronal tissues (e.g., smooth muscle and endothelium) compared with the surface area of the nerve terminals to which the NE in the incubation fluid can come in contact.

The concentrations of NE used in these studies are within the range of concentrations (1 nM–50 μM) estimated to be within synaptic clefts of blood vessels (20–22). The wide range of the estimates of NE concentrations in the cleft relate in part to the differences in cleft width in large and small blood vessels; the cleft appears to be wider in large vessels (23,24). No estimate of the NE concentration in synaptic clefts has been made in canine saphenous veins. When the vein is placed for a given time interval in incubation media containing NE, diffusion of NE into the synaptic cleft occurs and its removal is dependent upon the uptakes and subsequent metabolism. The present data indicate that the sites at which both neuronal uptake and extraneuronal uptake occur are readily accessible to the [^{3}H]NE that was present in the incubation fluid and that initial uptake was not slowed by a need to allow diffusion of the [^{3}H]NE to locations deep in the surface of the vessel. These data, therefore, suggest that our preparation has allowed us to effectively isolate the membrane–transport process so as to allow an accurate determination of the kinetic parameters associated with neuronal uptake. These parameters should apply to neuronal and extraneuronal uptakes after release of endogenous NE by nerve stimulation provided the processes for removal of NE do not distinguish between exogenous and endogenous sources of NE. The net gradient in NE concentrations across the tissue should be almost equal, but opposite in direction, for stimulation-induced NE release and NE in incubation fluid.

To our knowledge there have been no studies that have assessed halothane-induced changes in neuronal uptake in the saphenous vein by comparing K_m and V_{max} values obtained in control and in halothane-treated tissues. Based upon the lack of change in K_m, halothane did not significantly alter the ability of neuronal membrane sites to take up NE. Similarly, halothane apparently did not affect the number of active neuronal uptake sites because no significant change in V_{max} was observed with halothane. Inasmuch as 2.5% halothane is at the upper end of its clinical dose range, an effect with a higher halothane concentration would have little clinical meaning. It also seems unlikely, therefore, that the halothane-induced inhibition of 3,4-dihydroxyphenylglycol (DOPEG) formation described previously (25) can be attributed to decreased neuronal uptake. Because transmembrane access of NE to the intraneuronal enzyme monoamine oxidase (MAO) is apparently unaffected by halothane, then decreased DOPEG formation may be caused by inhibition of the enzyme itself. This possibility will be the subject of further investigation.

A possible source of error in this study deserves comment. It could be argued that some [^{3}H]NE taken up by the cocaine-sensitive uptake system was deaminated to DOPEG that effluxed out of the neuron (4), thereby decreasing our estimate of total uptake. A significant alteration due to this effect seems unlikely because the incubation time employed (1 min) is substantially less than the reported half-time (22 min) for DOPEG efflux (26).

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Prolongation of Lidocaine Spinal Anesthesia with Epinephrine and Phenylephrine

Craig H. Leicht, MD, MPH, and Stephen A. Carlson, MD

LEICHT CH, CARLSON SA. Prolongation of lidocaine spinal anesthesia with epinephrine and phenylephrine. Anesth Analg 1986;65:365–9.

The effect of vasoconstrictors on the duration of lidocaine spinal anesthesia is controversial. We conducted a double-blind study of 28 neurologically normal ASA Class I or II patients to determine the effect of vasoconstrictors (epinephrine and phenylephrine) on the duration of lidocaine spinal anesthesia. The patients were randomized into three groups. All patients received 1.2 mg lidocaine per inch body height, mixed with 0.5 ml of test solution. Group 1 patients received lidocaine plus 0.5 ml normal saline; Group 2 patients received lidocaine plus 0.3 mg epinephrine; Group 3 patients received lidocaine plus 5 mg phenylephrine. Segmental sensory blockade was assessed by pinprick at 2-min intervals for the first 20 min and then every 5 min thereafter. Mean highest level was between T-2 and T-3 for all 3 groups. Time from injection to highest sensory level was similar in Groups 1 and 3, 11.6 ± 3.57 and 12.0 ± 5.10 min, respectively, but was significantly prolonged in Group 2, 18.1 ± 4.33 min. Time for regression by two sensory dermatomes were significantly prolonged in both Groups 2 and 3, 102.9 ± 18.1 and 105.7 ± 33.1 min, respectively, compared to 78.1 ± 12.6 min in Group 1. Times for regression to T-12 was also significantly prolonged in both Groups 2 and 3, 153.7 ± 27.6 and 156.8 ± 26.7 min, respectively, compared to 117.71 ± 10.0 min in Group 1. In the doses used in the present study, both epinephrine and phenylephrine significantly prolong the duration of lidocaine spinal anesthesia.

Key Words: ANESTHETIC TECHNIQUES—spinal.

Vasoconstrictors, usually epinephrine or phenylephrine, are frequently added to local anesthetics to prolong the duration of spinal anesthesia. Although these agents have been used for this purpose for many years (1–4), their efficacy is still controversial. The duration of tetracaine spinal anesthesia has been shown to be prolonged by either epinephrine or phenylephrine (3–5), but the effects of vasoconstrictors on duration of lidocaine spinal anesthesia is controversial both in animals and in humans (6–11). We present a randomized double-blind study comparing the effect of epinephrine and phenylephrine on the duration of lidocaine spinal anesthesia in humans.

Methods

We studied 28 neurologically normal ASA Class I or II patients between the ages of 18 and 60, undergoing lower abdominal surgery in the supine position. Informed consent from all patients and institutional approval for the study was obtained. All patients received diazepam, 10–15 mg orally, as premedication 60 min before the surgical procedure. Five hundred to 1000 ml of balanced salt solution was infused, and glycopyrrolate, 200 μg, was administered intravenously prior to the induction of spinal anesthesia. All patients were monitored with an ECG and blood pressure cuff.

After initial vital signs were recorded, the patients were placed in the lateral decubitus position with the operative side in the dependent position. Utilizing sterile technique, a lumbar puncture was performed at the L2-3 interspace, using a midline approach, with a 25-g spinal needle passed through an 18-g introducer. The appearance of free-flowing, clear cerebral spinal fluid in the hub of the spinal needle indicated proper needle placement. After injection of the an-

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The opinions or assertions expressed in this paper are those of the authors and are not to be construed as official or as necessarily reflecting the views of the Department of the Navy or the naval service at large.

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Address correspondence to Dr. Leicht, c/o Clinical Investigation Department, Naval Hospital, San Diego, CA 92134-5000.

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Table 1. Patient Characteristics

Patient variables	Group 1 (lidocaine ± normal saline)	Group 2 (lidocaine + 0.3 mg epinephrine)	Group 3 (lidocaine + 5 mg phenylephrine)
Sex (number)			
Female	0	0	0
Male	9	10	9
Age (yr)			
Mean	32.3	28.6	22.2*
Range	19–60	18–41	19–32
Weight (kg)			
Mean	74.8	73.5	79.0
Range	61–86	60–107	59–95
Height (in)			
Mean	68.8	68.4	70.6
Range	65–75	66–74	66–75

*Significantly different ($P < 0.05$) from group 1 and group 2 by analysis of variance for comparison among multiple groups and by Student's *t*-test for unpaired data.

esthetic solution, the introducer and spinal needle were removed, and the patient was immediately placed in a supine horizontal position. All patients received 1.2 mg lidocaine (5% xylocaine in 7.5% glucose) per inch of body height mixed with 0.5 ml of the test solution. To insure freshness of the test solutions and facilitate double blindness, the test solutions were prepared and coded by the clinical pharmacy on the morning of the procedure. The patients were randomized into three groups by a computer program which generated random numbers. Group 1 patients received lidocaine plus 0.5 ml normal saline. Group 2 patients received lidocaine plus 0.3 mg epinephrine. Group 3 patients received lidocaine plus 5 mg phenylephrine. Segmental sensory blockade was assessed by response to pinprick at 2-min intervals for the first 20 min and thereafter at 5-min intervals until regression to at least T-12 level. Motor blockade was not assessed due to the difficulty of accurate measurements in the thoracoabdominal area. Blood pressure and heart rate were recorded at 2-min intervals for the first 30 min, at 5-min intervals for the remainder of the procedure, and every 15 min postoperatively. Systemic vasopressors were administered if the systolic blood pressure decreased 20–30% below preanesthetic values or if systolic blood decreased below 90 torr. The highest sensory level was recorded, and the following values were calculated: 1) time from injection to highest level; 2) time for two-segment regression of the level of anesthesia; and 3) time for regression to T-12 level. Mean values and standard deviations were calculated for each group and compared using analysis of variance for comparison between multiple groups and the Student's *t*-test for unpaired data. A value of $P < 0.05$ was considered statistically significant.

Results

No significant difference existed with regard to height, weight, or sex distribution in the three groups (Table 1). However, the mean age of patients in Group 3 (22.2 yr) was significantly less than in Groups 1 and 2 (31.1 and 28.6 yr, respectively). There were no significant cardiovascular changes in any patients. Among the three groups, no significant differences existed in the highest sensory level of anesthesia achieved, the mean highest level being between T-2 and T-3 in all groups. The time between injection and achievement of the highest sensory level (termed onset or latency by previous investigators) was similar in Groups 1 and 3, 11.6 ± 3.57 and 12.0 ± 5.10 min, respectively, but it was significantly prolonged in Group 2, 18.1 ± 4.33 min (Table 2, Fig. 1). The time for regression of the level of anesthesia by two sensory dermatomes was significantly greater in Groups 2 and 3 (102 ±

Table 2. Sensory Levels after Intrathecal Administration of Lidocaine with or without Vasoconstrictors

Anesthesia used	Time from injection to highest level (min)	Time for two-segment regression (min)	Time for regression to T-12 (min)
Lidocaine + normal saline	11.6 ± 3.57	78.1 ± 12.6	117.7 ± 10.0
Lidocaine + 0.3 mg epinephrine	18.1 ± 4.33*	102.9 ± 18.1	153.7 ± 27.6*
Lidocaine + 5 mg phenylephrine	12.0 ± 5.10	105.7 ± 33.1*	165.8 ± 26.7*

*Significantly different ($P < 0.05$) from lidocaine with saline by analysis of variance for comparison among multiple groups and by Student's *t*-test for unpaired data.

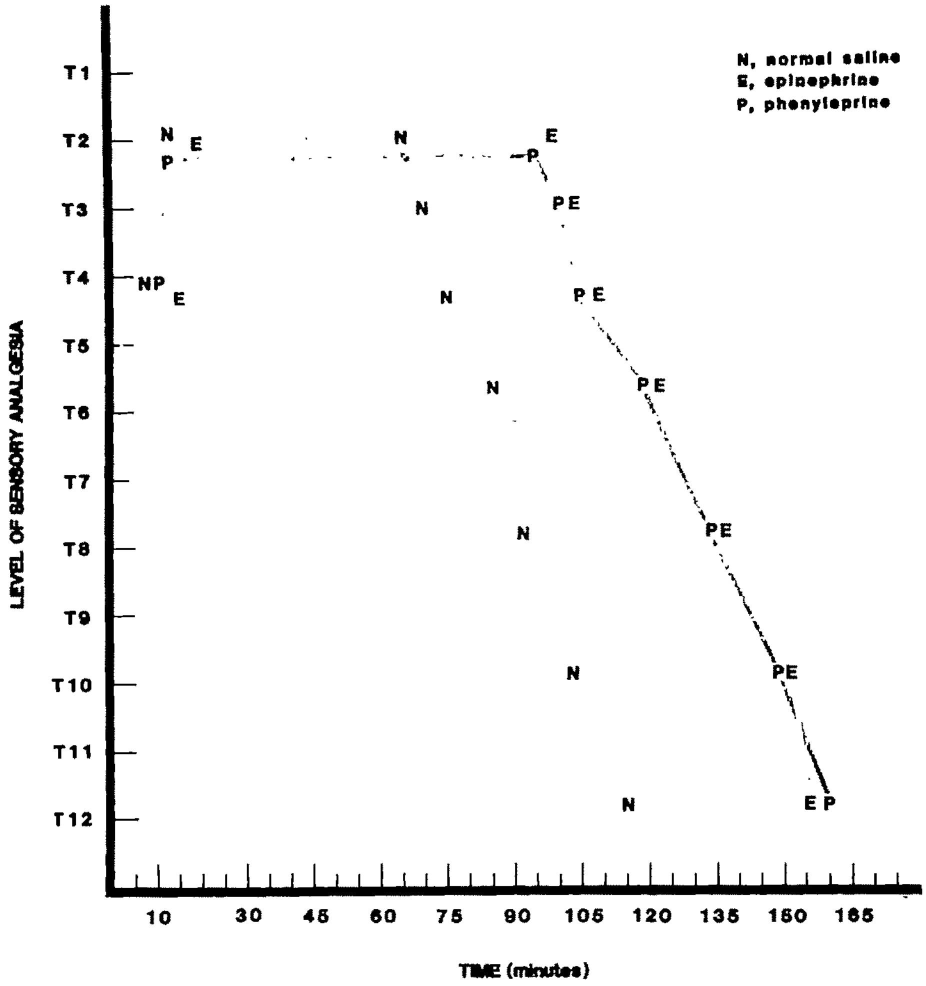

Figure 1. Mean height and duration of anesthesia.

18.1 and 105.7 ± 33.1 min, respectively) than in Group 1 (78.1 ± 12.6 min) (Table 2, Fig. 1). The time for regression of the level of anesthesia to T-12 was also significantly greater in Groups 2 and 3 (153.7 ± 27.6 and 156.8 ± 26.7 min, respectively) than in Group 1 (117.71 ± 10.0 min) (Table 2, Fig. 1). There was no significant difference between Groups 2 and 3 with regard to two-segment regression or regression to the T-12 level (Table 2, Fig. 1).

Three patients in Group 1 required intraoperative sedation because of pain at the operative site near the end of the surgical procedure. These patients were retained in the study as long as they continued to respond appropriately to questioning and were able to easily discriminate sharp vs dull pinprick. Additionally, one of these patients required local infiltration at the operative site and eventual general anesthesia, after which point no further data were collected. In contrast, no patients in Group 2 or 3 required intraoperative supplementation of analgesia. Although this is an interesting qualitative difference, no conclusions should be drawn from this finding because length of operation could not be controlled for each of the groups.

Discussion

Epinephrine and phenylephrine, when added to tetracaine for spinal anesthesia, have been shown to prolong the duration of sensory and motor blockade (3–5). There is no general agreement, however, on the effect of added vasoconstrictors to lidocaine spinal anesthesia (6–11). Our study showed that effective doses of epinephrine and phenylephrine prolong clinically useful sensory analgesia with lidocaine spinal anesthesia as measured by time of two-segment regression and time of regression to a T-12 level. There were no significant differences in duration between the epinephrine and phenylephrine groups, and both appear to provide a useful spinal anesthetic of "intermediate" duration. Because the time from injection to highest dermatome level was significantly more rapid with phenylephrine than with epinephrine, phenylephrine may prove to be the agent of choice for prolongation of lidocaine spinal anesthesia.

The dose of lidocaine used in the study was chosen empirically; a lidocaine dosage of 1.2 mg per inch of body height seems to reliably produce dense sensory blockade to approximately the T-4 dermatome. The doses of epinephrine (0.3 mg) and phenylephrine (5 mg) were chosen because they represent the range of doses used in previous studies (5,6,10). The results of the present study are in agreement with that of Vaida et al (10), in which phenylephrine (2 mg and 5 mg) was shown to significantly prolong lidocaine spinal anesthesia. Denson et al. (7,8), using a rhesus monkey model, reported no prolongation of sensory analgesia with either epinephrine (0.2 mg) or phenylephrine (1.5 mg) when added to lidocaine for spinal anesthesia. Chambers et al. (6) studied the effects of adding 0.1, 0.2, or 0.3 ml of 1:1000 epinephrine to 1.5 ml of 5% lidocaine in 7.5% dextrose for spinal anesthesia and found no prolongation of two- and four-segment regression time. However, they did note an increase in time to total recovery in the epinephrine groups. Spivey (11) recently reported the effect of adding 0.2 mg epinephrine to 5% lidocaine in 7.5% dextrose for spinal anesthesia in term parturients undergoing cesarean section. He reported no increase in duration of analgesia as measured by the time for two-segment regression.

The present study differs from that reported by Chambers et al. (6) in several ways. First, the average age of patients in our study was 28 yr and in Chambers's study, 64 yr. In a recent review article, Greene (12) states that age is a chief influence on the rate of absorption of local anesthetics used in spinal anesthesia. As a result, duration of spinal anesthesia is prolonged in the older patient. Therefore one could postulate that any additional effect of epinephrine on the duration of lidocaine spinal anesthesia might be minimized in the older age group. Furthermore, the concentration of lidocaine in Chambers's control group was greater than in the study groups where the lidocaine was diluted by the addition of epinephrine. For example, the lidocaine concentration in the control group was 5%, whereas in the 0.3 mg epinephrine group it was 4.15%. In the present study, the concentration of lidocaine in all groups was constant.

Another important difference is that all patients in Chambers's study received the same dose of lidocaine, regardless of their height. Administering a single, standard dose of local anesthetic to all patients can result in marked differences in the milligram dose:spinal segment ratio for each of the subjects. Despite reporting no difference in mean height among the groups, it is likely that there was individual variation in height within each group. This variance in lidocaine dose:spinal segment ratio would tend to mask the effect of epinephrine on the duration of spinal anesthesia as potentially significant differences would be obscured due to regression toward the mean.

Other possibly significant ways in which these studies differ include the following: 1) patient position, lithotomy in Chambers's study and supine in our study; 2) mean highest level of analgesia was higher in our study, T-2 compared to T-7; and 3) the baricity of the local anesthetic solution differed among Chambers's groups because each group was given different volumes of epinephrine, whereas, in our study, equal volumes of either normal saline, epinephrine, or phenylephrine were added to the local anesthetic solution.

Our study also differed significantly from Spivey's study in several ways. Most obvious and probably most significant, is that all patients in Spivey's study were term parturients. The many physiologic changes of pregnancy include significant changes in subarachnoid and epidural volumes and blood flows. Second, the local anesthetic dose (40 mg lidocaine) used by Spivey was much less than that used in our study (mean for all patients, 86 mg lidocaine). As Spivey points out in his article, the use of such a low dose of local anesthetic could result in a "high, thin block." In this situation, the duration of the highest sensory level achieved could be shorter than a comparable, more dense sensory level achieved with a larger dose. Here again it is difficult to compare the effect of epinephrine on the duration of analgesia because the blocks may differ in character. Again, as in Chambers's study, Spivey used the same lidocaine dose regardless of the patient's height. In any case, it is unreasonable to extrapolate Spivey's results to nonpregnant patients.

The mechanism for prolongation of spinal anesthesia by the addition of vasoconstrictors is unclear. Decreased vascular uptake does not appear to be the mechanism (13). Converse et al. (14) showed that epinephrine, in spite of prolonging the duration of tetracaine spinal anesthesia, had no effect on the rate of disappearance of tetracaine from the cerebral spinal fluid. Denson et al. (7,8) demonstrated no difference in the rate of absorption of lidocaine solutions from the cerebral spinal fluid, with or without epinephrine or phenylephrine. Recent research suggests that adrenergic modulation of spinal cord activity may be an important factor in the transmission of pain information in the spinal cord. Collins et al. (15), using the decerebrate, spinal cord-transected cat model, found epinephrine suppressed noxiously evoked activity in wide dynamic range neurons in the dorsal horn of the spinal cord. (Wide dynamic range neurons are those that respond with increased firing frequency to skin stimulation over a wide range of intensity; maximum response occurs with noxious stimuli such as heat.) Vasoconstrictors may act directly on the spinal cord to enhance or prolong spinal anesthesia. The role of epinephrine and phenylephrine as modulators of neurotransmission is one hypothesis for the prolongation of spinal anesthesia by vasoconstrictors.

In summary, when added to lidocaine spinal anesthesia, both epinephrine (0.3 mg) and phenylephrine (5 mg) significantly prolonged analgesia as measured by two-segment regression, as well as time of regression to the T-12 dermatome. Both appear to provide a clinically useful spinal anesthetic of "intermediate" duration.

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Effects of Alfentanil and Fentanyl on Common Bile Duct Pressure

Markku J. Hynynen, MD, Markku T. Turunen, MD, and Kari T. Korttila, MD

HYNYNEN MJ, TURUNEN MT, KORTTILA KT. Effects of alfentanil and fentanyl on common bile duct pressure. Anesth Analg 1986;65:370–2.

The effects of alfentanil (7.5 or 15 µg/kg) and fentanyl (1.5 µg/kg) on common bile duct pressure were examined by using an indwelling postoperative T-tube in 36 conscious, unpremedicated patients. All opiate doses significantly ($P < 0.001$) increased the pressure. There was no significant difference among the groups in the peak pressures nor in the times to peak pressures. Fentanyl had a significantly longer duration of effect on pressure.

Key Words: ANALGESICS—alfentanil, fentanyl. LIVER—biliary tract pressure.

Fentanyl has been shown in numerous studies to increase the common bile duct pressure (1–7). The biliary tract effects of alfentanil, a fentanyl derivative with a shorter duration of action than that of its congener (8,9), have not been reported. Therefore we compared the effects of these two analgesics on the intrabiliary pressure in conscious patients with an indwelling T-tube. Furthermore, because a dose-related increase in the intracholedochal pressure has been demonstrated with morphine and fentanyl (4,10,11), we studied the effects of two small doses of alfentanil on the biliary pressure.

Materials and Methods

Patients and Equipment

Thirty-six patients, each of whom had undergone exploration of the common bile duct and had had a T-tube installed postoperatively in the common duct, were studied 7–13 days after the operation by use of the indwelling tube. Informed consent was obtained, and the study was approved by the institutional ethics committee.

All patients had normal postoperative cholangiograms and asymptomatic tolerance to the T-tube clamping for at least 12 hr. No spasmolytic or analgesic agents or drugs known to affect the sphincter of Oddi were given during a 12-hr period before the measurements.

The measurements were performed by a modification of the technique described by Tuominen (12). The intracholedochal pressure was measured during a continuous infusion of balanced salt solution administered with an infusion pump (Perfusor, B. Braun-Melsungen) into the T-tube using a 3-way stopcock and an appropriate extension tube. The rate of infusion did not increase the pressure in the system (55 ml/hr or less). The same stopcock was used to connect the T-tube both to an amplifier (Olli 224, Ollituote Oy, Finland) and a pressure transducer (AE 840, Aksjeselskapet Mikroelektronik, Norway). The transducer was zeroed to the midthoracic level. The pressure was recorded continuously for 45 min after administration of the test drugs with an ink-jet recorder (Mingograf 804, Siemens-Elema, Sweden). The pressure curve was read at the end-expiratory phase of ventilation.

After baseline recording of the bile duct pressure, 0.03 ml/kg of the test drug was administered intravenously over a period of 2 min in a double-blind, random fashion from coded ampules. The patients received either alfentanil (Orion Pharmaceutical, Finland), 7.5 or 15 µg/kg, or fentanyl (Fentanyl®, Orion Pharmaceutical, Finland), 1.5 µg/kg. Before admintration of the test drugs, the patients were asked to tell the investigators about any side effects they experienced during or after injection of the opiates.

Statistics

The demographic data and the control pressure values were compared among the groups with a one-way analysis of variance. The Friedman two-way analysis of variance and the Kruskal–Wallis one-way analysis of variance were used for statistical evaluation of the intra- and intergroup changes, respec-

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Address correspondence to Dr. Hynynen, Department of Anaesthesia, Helsinki University Central Hospital, Haartmaninkatu 4, SF-00290 Helsinki, Finland.

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Table 1. Demographic Data[a]

	Drug dose (μg/kg)		
	Alfentanil, 7.5	Alfentanil, 15	Fentanyl, 1.5
n (female/male)	11/3	8/3	9/2
Age (yr)	61 (26–82)	55 (24–81)	65 (43–81)
Weight (kg)	71 (60–86)	74 (50–100)	71 (43–98)
Height (cm)	165 (155–180)	165 (150–185)	164 (154–181)

[a]Number of patients or mean values with ranges.

tively. *P* values less than 0.05 were considered statistically significant.

Results

The groups were comparable in terms of demographic data (Table 1). There were no statistically significant differences in the baseline values of the intracholedochal pressures among the groups (Table 2). Changes from control common bile duct pressures are shown in Figure 1. All doses of opiates caused significant increases in the pressure ($P < 0.001$). There were no significant differences among the groups in the peak increase of the pressure or in the time to peak pressure (Table 2). Fentanyl had a longer duration of action as demonstrated by the significant difference in the changes from baseline among the groups from 9 to 15 and at 19 and 20 min after start of drug administration.

All patients felt euphoric and somewhat sedated during the action of the drug. One patient given 15 μg/kg alfentanil, an 81-yr-old woman, had to be aroused for a few minutes after drug administration because her spontaneous respiratory rate decreased to 5 breaths/min. Other side effects are presented in Table 3.

Discussion

In this study we have shown that the peak increases in common bile duct pressure in patients given either alfentanil or fentanyl are similar, but that the biliary tract effect of alfentanil wears off faster than that of fentanyl.

The previous results of the peak effects with equianalgesic doses of different opiate agonists are conflicting. Tuominen (12) found a statistically significant difference between anileridine and meperidine in conscious patients with a postoperative T-tube, but the effects of fentanyl, morphine, or meperidine did not differ significantly from each other in anesthetized humans (3,6) or guinea pigs (4). In this study, the maximal increase in the pressure, measured after two fairly similar opiate derivatives, alfentanil and fentanyl, did not differ significantly among the groups.

Our results with fentanyl are consistent with those of earlier studies, in which common bile duct pressure changes were measured postoperatively through an indwelling T-tube. A mean peak increase of 160–190% of the control value within about 5–7 min has been observed (2,7), compared to the increase of 164% measured 6 min after the completion of drug injection in this study.

The shorter duration of action of an alfentanil bolus than that of fentanyl (8,9) could be confirmed in this study by the statistically significant difference in the pressure increase among the groups from 9 to 15–20 min after drug administration. The peak opioid effect is reached more rapidly with alfentanil than with fentanyl (8,9). We did not, however, find any statistically significant difference in the time-to-peak effect on common bile duct pressure among the groups, although the effect seemed to appear earlier in both alfentanil groups than in the fentanyl group. In addition, earlier studies have shown that in spite of different durations of action, opiates may have a rather similar time-to-peak effect on biliary pressures (7,13).

We have recently suggested that the analgesic potency of the fentanyl dose used in this study is between the two alfentanil doses used (14). Therefore the bile duct pressure responses to the narcotic analgesics used seemed to be independent of the an-

Table 2. Common Bile Duct Pressures[a]

Drug dose (μg/kg)	Baseline (mm Hg)	Peak pressure increases (mm Hg)	Time to peak pressures (min)
Alfentanil, 7.5	8 ± 1	9 ± 1	6 ± 1
Alfentanil, 15	8 ± 1	8 ± 1	5 ± 1
Fentanyl, 1.5	7 ± 1	11 ± 1	8 ± 1

[a]Mean values ± SEM.

Table 3. Frequency of Side Effects[a]

	Drug dose (μg/kg)		
Side effect	Alfentanil, 7.5	Alfentanil, 15	Fentanyl, 1.5
Abdominal discomfort or colic-like pain	2	—	—
Nausea	—	1	—
Vomiting	—	—	1
Sweating	—	2	1
Shivering	—	—	1
Dry mouth	—	1	—

[a]Number of patients.

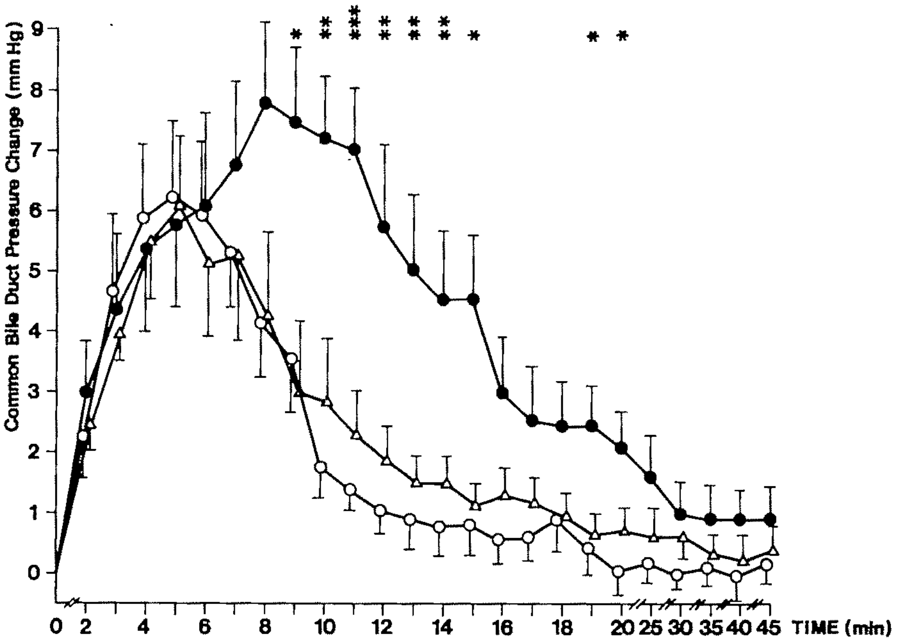

Figure 1. Changes in common bile duct pressure after administration of alfentanil, 7.5 (○) and 15 (△) μg/kg, and fentanyl, 1.5 (●) μg/kg (mean values ± SEM). Statistically significant differences in changes from baselines among the groups are indicated as follows: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$.

algesic potency of the drug bolus. Although a dose-related decrease in the bile duct flow and an increase in the intrabiliary pressure have been observed in anesthetized animals with a wide range of morphine and fentanyl doses (4,10,11), we could not demonstrate any difference in the time courses of the pressure changes in the alfentanil groups in spite of doubling the drug dose. This suggests that, at least in the dose range tested, alfentanil has no dose–response effect on the sphincter of Oddi and that the response in the bile duct pressure appears to be an "all or nothing" type of reaction. Because the response of common bile duct pressure to the narcotics we tested was pronounced in some patients and mild in others, considerable interindividual variations and unpredictable responses were noted, as was earlier reported to be the case with anileridine and meperidine (12).

In conclusion, alfentanil and fentanyl induced similar peak increases in the common bile duct pressure in postoperative patients within similar times. However, the effect of fentanyl lasted longer than that of alfentanil. Alfentanil had no dose-related effect in the small dose range studied.

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Succinylcholine Pretreatment with Magnesium Sulfate

M. F. M. James, MB, ChB, FFARCS, R. C. Cork, MD, PhD, and J. E. Dennett, SRN

JAMES MFM, CORK RC, DENNETT JE. Succinylcholine pretreatment with magnesium sulfate. Anesth Analg 1986;65:373–6.

The effect of pretreatment with 60 mg/kg magnesium sulfate on the neuromuscular blockade and consequent potassium release produced by 1.5 mg/kg succinylcholine in ten normal patients was compared with ten saline pretreated control patients. Magnesium had no significant effect on the characteristics of the paralysis. In control patients, serum potassium increased by an average of 0.57 ± 0.20 (SEM) mmol/L. No patient in the magnesium group had an increase in serum potassium (mean change −0.05 ± 0.02 mmol/L). The difference between the groups was statistically significant (P < 0.01).

Key Words: IONS—magnesium, potassium. NEUROMUSCULAR RELAXANTS—succinylcholine.

Magnesium sulfate has been used for many years in the management of convulsions in pregnancy-induced hypertension (1). Magnesium is widely known to potentiate the action of the nondepolarizing relaxants (2,3), but its interactions with succinylcholine have received scant attention. Several authors have reported prolonged duration of blockade and reduced requirements for succinylcholine when magnesium is used as a continuous infusion in pregnant patients (2–6). Fasciculations have also been reported not to occur in such patients (7). However, there are no reports of the effect of magnesium on the speed of onset of succinylcholine, or of the quality of the block achieved in magnesium-treated patients.

At the motor endplate, magnesium inhibits the release of acetylcholine, and at plasma levels above 5 mmol/L magnesium may produce neuromuscular blockade. Magnesium also decreases the sensitivity of the motor endplate to applied acetylcholine and decreases the force of contraction of muscle in response to direct electrical stimulation (8,9). Preventing the release of neurotransmitter should not interfere with the action of succinylcholine. However, the reduction in receptor sensitivity might interfere with the speed of onset and quality of relaxation produced by succinylcholine in much the same way as dose pretreatment with a nondepolarizing relaxant, but the direct effect on the muscle fiber might enhance the block. Delayed onset, reduced effectiveness of neuromuscular blockade, or both would increase the risk of regurgitation in the pregnant patient. On the other hand, a reduction in the severity of fasciculations might reduce the increase in intragastric pressure and add to patient safety.

The present study was designed to evaluate the effect of a single bolus dose of magnesium sulfate on the speed of onset of the relaxation produced by succinylcholine, the intensity of blockade, and the duration of paralysis. In view of the suggestion by Aldrete et al. (10) that magnesium prevents the increase in potassium produced by succinylcholine, we also evaluated the effect of magnesium on the hyperkalemic response to succinylcholine.

Methods

This study was approved by the hospital committee on ethics. Twenty ASA I patients scheduled for routine elective surgery were randomly allocated to a treatment or a control group. All subjects gave informed consent to the study.

Neuromuscular transmission was assessed by both Electromyogram (EMG) recording and by measurement of the twitch strength of the adductor pollicis muscle in response to supramaximal stimulation of the ulnar nerve at the elbow. Electromyogram recordings were made using a Medelec MS6 System (Medelec, Woking, England), which enabled continuous display of the amplitude of the electrical signal recorded from the muscle. No standard equipment was available for the measurement of twitch height, and so a specially constructed device was used. A syringe with a ring fitting on the plunger was mounted

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Address correspondence to Professor James, Department of Anaesthesia, Hillbrow Hospital, PO Box 23140, Joubert Park, Johannesburg, South Africa.

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onto a metal frame into which the subject's right hand could be firmly fixed. The syringe was filled with saline, and connected to a Hewlett Packard pressure transducer (HP 1280C), pressure module (HP 8805D) and recorder (HP 7754A) (Hewlett Packard, Waltham, Massachusetts). Changes in muscle tension were then recorded as pressure changes on the recorder. Satisfactory recordings of twitch height with minimal baseline drift were obtained by these means.

All patients were given 0.15 mg/kg of diazepam orally for premedication 1 hr before entry to the induction room. On arrival in the induction room, a cannula was inserted into a vein on each arm, one for the administration of drugs, and the other for taking blood samples. Stimulating electrodes were attached to the skin over the ulnar nerve at the elbow, and recording electrodes placed over the adductor pollicis muscle in the manner described by Ali and Savarese (11). An earthing strip was placed around the forearm to prevent the stimulating current from being conducted over the skin and detected by the recording electrodes. The patient's hand was placed in the frame, and the ring of the syringe placed over the base of the thumb. The volume of saline in the syringe was adjusted so that the thumb was held at about 60 degrees to the index finger, and the angle of the syringe adjusted so that the plunger was in a direct line with the movement of the thumb.

Sodium thiopental was administered until the eyelash reflex was lost. Nitrous oxide with 30% oxygen was administered by face mask and ventilation gently taken over by hand. Stimulation was commenced with a pulse duration of 0.2 sec and a voltage of 150 volts at a rate of 2 Hz, and the EMG and twitch height continuously recorded throughout the experiment. Baseline measurements of serum magnesium and potassium levels were made at this point. Patients in the experimental group were then given 60 mg/kg of magnesium sulfate as a 50% solution by slow intravenous injection over 1 min. Further blood samples were taken. To ensure adequate levels of anesthesia during intubation, a further bolus of 50% of the induction dose of thiopental was given at this point. Succinylcholine, 1.5 mg/kg, was given, and after 60 sec the trachea was intubated. The severity of fasciculations was recorded on a scale of 0 to 3: 0 for the absence of fasciculations, 1 for mild twitches involving face and fingers only, 2 if the fasciculations involved the limbs or trunk, and 3 if the fasciculations produced gross body movements. Blood samples were taken again 2 min after succinylcholine administration. Anesthesia was maintained with nitrous oxide and oxygen, supplemented by additional increments of thiopental as needed, until 90% recovery of twitch and EMG voltage had been achieved. Times to 90% depression of twitch height and to 90% recovery were noted.

Data were analyzed using Student's *t*-test for grouped data with the Bonferroni modification for multiple comparisons when appropriate. Significance was defined as $P < 0.05$. Results are presented as means ± SEM.

Table 1. Baseline Values (Means ± SEM) in the Magnesium and Control Groups

	Magnesium	Control
Age (yr)	30.3 ± 3.0	27.6 ± 1.3
Height (cm)	163.2 ± 4.8	168.1 ± 5.8
Weight (kg)	62.8 ± 4.0	65.9 ± 2.8
K^+ (mmol/L)	3.91 ± 0.10	3.89 ± 0.22
Mg^{++} (mmol/L)	0.91 ± 0.06	0.96 ± 0.05
Twitch (mm)	20.9 ± 4.6	23.9 ± 3.1
EMG (mV)	8.5 ± 3.0	8.0 ± 0.4

Abbreviation: EMG, electromyogram.

Results

There were no significant differences in the age, height, or weight of the two groups. Baseline serum levels of potassium and magnesium, twitch height, and EMG voltage were similar in both groups (Table 1).

The serum magnesium level was increased to a mean value of 3.6 ± 0.35 mmol/L at the end of the infusion. This decreased to 2.9 ± 0.69 mmol/L after intubation, approximately 4 min later.

After magnesium pretreatment, there was a variable reduction in twitch height and EMG voltage that depended on the level to which the serum magnesium increased. In subjects in whom the serum magnesium increased less than 3 mmol/L, there was no reduction in twitch height, but some neuromuscular block was noted at values greater than this. Where a demonstrable block occurred, this was partially reversed by succinylcholine, before the paralysis ensued (Fig. 1). In only one case was the reduction of twitch height greater than 20% of the control. In this patient, the serum magnesium level was 5.2 mmol/L, possibly due to a relative overdose being given to a moderately obese patient (85 kg) using the mg/kg dosage schedule.

After administration of succinylcholine, there was no difference in the speed of onset of the neuromuscular blockade in the two groups. A 90% depression of twitch height was achieved in 25.0 ± 2.1 sec in patients given magnesium and in 27.6 ± 3.6 sec in control patients. Recovery time to 90% of control twitch height was 450.6 ± 103.1 sec in the magnesium group and 569.6 ± 125.6 sec in controls, a difference that

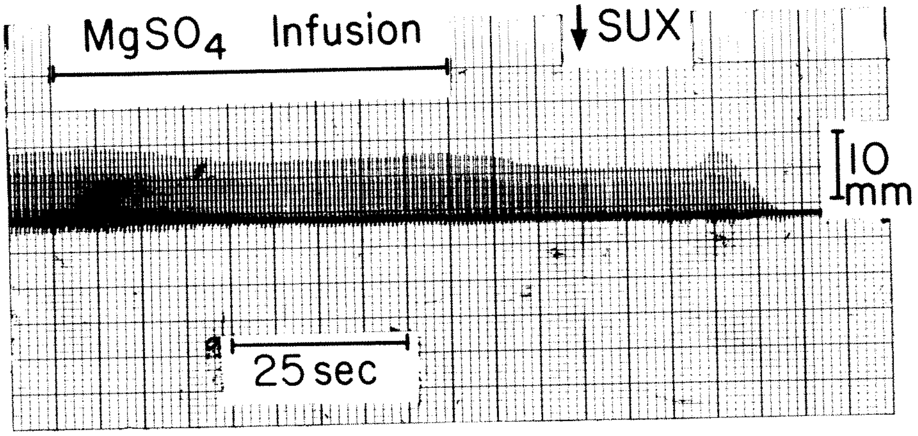

Figure 1. Magnesium infusion produced a moderate conduction block in some patients that was partially reversed by succinylcholine before the onset of paralysis. In this example, there is a 30% reduction in twitch height after magnesium infusion, which is momentarily reversed by succinylcholine; 90% depression of twitch height occurred in 28 sec. Twitch height is in millimeters, and paper speed is 1.25 mm/sec.

was not statistically significant. There were no significant differences between the changes in twitch height and those in the EMG recordings at any stage in the experiment. Good intubating conditions were present in all cases.

Fasciculations were absent in four patients of the magnesium group and in two of the control group. Grade 3 fasciculations occurred in three patients in the control group and none of the magnesium group. The difference in the incidence and severity of fasciculations in the two groups did not reach statistical significance.

In control patients serum potassium increased an average of 0.57 ± 0.20 mmol/L ($P < 0.05$) after the administration of succinylcholine (Table 2), with eight out of ten subjects showing an increase. In patients given magnesium, there was no increase in serum potassium in any patient after succinylcholine administration. The difference between the groups in changes in serum potassium after succinylcholine administration was statistically significant ($P < 0.01$).

Discussion

No interference with the onset or intensity of the succinylcholine blockade was encountered, and good intubating conditions were achieved in all cases. In contradistinction to other reports (2,3,6), no prolongation of the block occurred in patients given magnesium. Several explanations for this finding are possible. The first is that we simply did not detect the effect due to the very large range of recovery times found. However, the fact that the mean recovery time in patients given magnesium appeared to be shorter than that in control patients tends to belie this possibility. An alternative explanation is that rapid clearance of magnesium after a single intravenous bolus meant that the level of serum magnesium was too low to affect the block by the time the succinylcholine was wearing off. Magnesium levels were not measured at the time of recovery. Because the previous reports dealt mainly with long-term administration of magnesium in pregnancy-induced hypertension, it is possible that tissue levels of magnesium were higher in these other studies than in the present one, with consequent prolongation of the block. This possibility is supported by the failure of magnesium to abolish fasciculations in our study, whereas fasciculations have been reported to be absent in patients with pregnancy-induced hypertension treated with magnesium (7). Whatever the correct explanation, in this study, prior administration of a bolus of magnesium sulfate interfered surprisingly little with the neuromuscular blockade produced by succinylcholine.

This study confirms the work of Aldrete et al. (10) that magnesium can abolish the increase in potassium that accompanies the use of succinylcholine. In a recent report, Magee and Gallagher (12) showed that a "self-taming" dose of succinylcholine abolished the increase in potassium induced by succinylcholine, and they suggested that no other method was as reliable in preventing the hyperkalemic response to succinylcholine. However, no patient in the present study or in the report by Aldrete et al. showed any increase in potassium after succinylcholine administration when magnesium was given. The ability of magnesium to inhibit potassium release after succinylcholine is not entirely surprising. Magnesium prevents potassium efflux from the myocardium in isolated rat hearts (13), lowers serum potassium levels in the intact dog (14), and prevents potassium efflux in the rat diaphragm (15). These effects have been ascribed to a direct effect of magnesium on potassium channels in the sarcolemmal membrane (16). Whether or not magnesium offers protection in circumstances in which the increase in serum potassium induced by succinylcholine is known to be hazardous is debatable, but it does appear to offer a potential benefit in this regard that

Table 2. Mean ± SEM Serum Potassium Values (mmol/L) in the Two Groups before and Two Minutes after Succinylcholine

Group	Before	After	Change
Magnesium	3.91 ± 0.10	3.86 ± 0.11	−0.05 ± 0.02
Control	3.89 ± 0.16	4.46 ± 0.34	0.57 ± 0.20*

*$P < 0.01$ for the difference between the groups.

deserves further attention. Magnesium would certainly appear to offer protection to the toxemic parturient who may be renally compromised.

Magnesium sulfate offers a rapid and effective means of controlling eclamptic convulsions. When magnesium is used prior to cesarean section, the anesthesiologist may safely employ succinylcholine without fear of either increased risk of regurgitation due to delay in onset of relaxation, or unduly prolonged paralysis. Fasciculations are unlikely to be severe, and as a fringe benefit, potassium rise is unlikely to occur. Investigators have suggested that the well-described transient hypotensive effect of intravenous magnesium (17) may be of benefit in hypertensive parturients if magnesium sulfate is infused immediately prior to induction of anesthesia (18). In the poorly controlled hypertensive parturient presented for emergency cesarean section, there may be considerable benefit to be gained from the administration of magnesium sulfate by the anesthesiologist at the time of induction; even when the blood pressure in such patients is well controlled, magnesium infusion may offer useful protection. Caveats regarding the use of nondepolarizing relaxants in magnesium-treated subjects must, however, still be observed.

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ANESTH ANALG 1986;65:377–80

Rate of Protamine Administration:

Its Effect on Heparin Reversal and Antithrombin Recovery after Coronary Artery Surgery

James R. Zaidan, MD, Steve Johnson, MD, Russell Brynes, MD, Sandra Monroe, MT, (ASCP), and Anita V. Guffin, MMSc

ZAIDAN JR, JOHNSON S, BRYNES R, MONROE S, GUFFIN AV. Rate of protamine administration: its effect on heparin reversal and antithrombin recovery after coronary artery surgery. Anesth Analg 1986;65:377–80.

Patients received a calculated dose of protamine at two different rates (5 min and 30 min) after coronary artery surgery to determine the relationship of the rate of protamine administration with the adequacy of heparin reversal and the rate of return of antithrombin III (AT III) activity. Plasma heparin concentrations and AT III activities were measured at specific times both during and for 3 days after cardiac surgery. Both rates of protamine administration resulted in clinically acceptable clotting, return of the activated coagulation time to normal, and zero heparin concentration after 24 hr. Two hours after protamine administration, patients who received rapidly administered protamine had prolonged coagulation compared to the other group. Normal AT III activity returned the second postoperative day. These results imply that normal postoperative coagulation occurs when protamine is administered over 30 min without a bolus, and that blood is potentially hypercoagulable immediately after heparin reversal because of depressed AT III activity.

Key Words: BLOOD, COAGULATION—heparin, protamine.

Predicting the appropriate heparin-reversing dose of protamine remains a complicated issue. Investigators advocate a number of predictive protocols, but in the clinical setting, inadequate reversal and possibly heparin rebound persist (1–4). Protamine dosage schedules based only on total dose do not consider the relationship between the rate of protamine administration and adequacy of heparin reversal. Protamine has hemodynamic side effects, especially in patients with poor left ventricular function, that might be circumvented by slow administration (5); however, our clinical impression is that slow administration of protamine does not produce adequate intraoperative clotting.

Also related to the pharmacology of heparin is antithrombin III (AT III) activity. In vitro studies utilizing immunoelectrophoretic and chromatographic techniques reveal that protamine binds to heparin and simultaneously restores AT III activity (6,7). These findings imply that AT III activity should balance excessive coagulation immediately after protamine administration. However, these studies did not measure AT III activity. Clinically, blood could be hypercoagulable if AT III activity remained subnormal after protamine administration. This investigation was performed to determine 1) the relationship between the adequacy of heparin reversal and the rate of protamine administration and 2) the time for normal AT III activity to return after cardiopulmonary bypass.

Methods

After Human Investigations Committee approval, 20 patients scheduled for elective coronary artery surgery gave their written informed consent to this study. The patients were randomly distributed into two groups. Patients in group 1 received a bolus of protamine over 5 min; those in group 2 received a 30-min constant infusion of protamine. The calculated dose of protamine for each patient was based on a 90-min decrease of one half of heparin's initial activity determined by the partial thromboplastin time, activated plasma partial thromboplastin time, whole blood ac-

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Address correspondence to Dr. Zaidan, Emory University Hospital, Department of Anesthesiology, 1364 Clifton Road, N.E., Atlanta, GA 30322.

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Table 1. Patient Characteristics

	Height (in)	Weight (kg)	Age (yr)	Grafts	CPB time (min)	Heparin dose (units)	Protamine dose (mg)	Preoperative ACT (sec)
Group 1	69.0 ± 2.6	80.6 ± 17.8	59.3 ± 7.8	3.2 ± 1.13	69.3 ± 21.3	33,300 ± 6378	193 ± 61	125 ± 14
Group 2	69.8 ± 3.4	78.3 ± 14.6	55.3 ± 11.1	2.8 ± 1.13	58.0 ± 17.4	32,150 ± 5764	197 ± 47	121 ± 10
P	0.7156	0.7559	0.3643	0.7878	0.2097	0.7680	0.4598	0.2025

Abbreviations: CPB, cardiopulmonary bypass; ACT, activated coagulation times.

Table 2. Postoperative Coagulation Studies Drawn During Measurement Period Ten

	Prothrombin time (sec)	Partial thromboplastin time (sec)	Lee-White coagulation time (min)	ACT* (sec)	Platelet count (× 10^3)	Hct
Group 1	16.0 ± 0.9	47.3 ± 19.2	13.8 ± 6.5	135 ± 8	143.7 ± 36.8	24.8 ± 4.7
Group 2	15.1 ± 0.6	33.7 ± 7.2	8.5 ± 4.0	123 ± 9	137.0 ± 33.0	26.5 ± 4.3
P	0.0183	0.0058	0.0425	0.003	0.6739	0.7942

Abbreviation: ACT, activated coagulation times.
*These studies were performed on sample 10 except for the ACT which was performed on sample 9.

Table 3. Cumulative Postoperative Blood Loss

	Blood loss, end of hr 1 (ml)	Blood loss, end of hr 4 (ml)
Group 1	200 ± 150	471 ± 240
Group 2	144 ± 52	349 ± 118
P	0.3847	0.2123

Table 4. Administered Blood Products

	Packed cells (ml)	Whole blood (ml)	Fresh frozen plasma (ml)	Platelets
Group 1	265 ± 434	100 ± 316	45 ± 142	0
Group 2	300 ± 283	250 ± 486	25 ± 79	0
P	0.5833	0.212	0.3688	—

tivated partial thromboplastin time, and Lee-White whole blood clotting time (8). Patients were excluded from the investigation if they were receiving anticoagulant or antiplatelet drugs, or if they had abnormal preoperative clotting studies. All of the patients received fentanyl–diazepam–relaxant anesthesia and 400 units of heparin/kg to initiate anticoagulation. Bentley BOS-105 oxygenators (Bentley Laboratories, Inc., Irvine, California) and the same composition of cardiopulmonary bypass (CPB) priming fluid and cardioplegic solution were used in all patients.

Radial arterial blood samples for measurement of plasma heparin concentration and AT III activity were drawn at the following times: 1) before induction of anesthesia; 2) after induction of anesthesia but before incision; 3) 5 min before heparin administration; 4) 5 min after completion of heparin administration; 5) 5 min and 6) 30 min after initiating CPB; 7) after CPB, and immediately before protamine administration; 8) 15 min, 9) 1 hr, and 10) 2 hr after completion of protamine administration; and 11) on postoperative day 1, 12) day 2, and 13) day 3. Relating sampling times to completion of protamine administration rather than heparin administration caused a 25-min delay in drawing blood from patients in group 2 in relation to patients in group 1. Prothrombin time (PT), partial thromboplastin time (PTT), Lee-White coagulation time, and platelet count were measured in blood drawn 2 hr after protamine administration (sample 10). The initial 5 ml of each blood sample were discarded to help to clear heparin from the arterial cannula. Activated coagulation times (ACT) verified adequacy of heparin dosage during CPB. A fluorometric method (Protopath, American Dade, Miami, FL) quantitated AT III activity and heparin concentration (9).

Intensive care unit personnel were not informed of the study so that standard blood replacement policies would not change. Postoperative blood loss was recorded 1 and 4 hr after admitting the patient to the intensive care unit.

Data are presented as the means ± SD. The Mann–Whitney U test or an analysis of variance were used to compare the groups. $P < 0.05$ was considered statistically significant.

Results

The patients' ages, heights, weights, duration of cardiopulmonary bypass, number of coronary artery grafts, heparin and protamine doses, and initial ACTs were not statistically different (Table 1). Postoperative coagulation studies are shown in Table 2. The PTT

Table 5. Plasma Heparin Concentration (units/ml plasma)

Sampling period	1–3	4	5	6	7	8	9	10	11–13
Group 1	0	9.98 ± 1.89	5.93 ± 1.46	5.68 ± 1.18	4.82 ± 1.57	0.22 ± 0.11	0.16 ± 0.13	0.07 ± 0.05	0
Group 2	0	9.57 ± 2.16	6.04 ± 1.39	5.98 ± 1.97	4.74 ± 1.16	0.05 ± 0.05	0.03 ± 0.05	0.07 ± 0.07	0

and Lee-White coagulation time were significantly longer in group 1 than in group 2. Although the prothrombin time was statistically longer in group 1, this difference was not clinically important. Mean ACT in group 1 after protamine also was statistically longer than that in group 2, but remained within normal limits (135 ± 8 sec). Clinical evidence of clotting appeared in all patients before mediastinal closure.

Blood losses were not significantly different in the two groups (Table 3). Postoperative volume replacement, outlined in Table 4, indicates that despite the longer coagulation times, PT, and PTT values noted in group 1, patients in this group did not require more blood products than those in group 2.

Plasma heparin concentrations were not statistically different. However, after protamine administration, heparin concentrations were higher in group 1 than group 2 in samples 8 through 10. Heparin concentrations were zero 24 hr after protamine administration. These results are shown in Table 5.

Antithrombin activity progressively decreased with each measurement period before cardiopulmonary bypass. The largest decrease in AT III activity occurred with initiation of CPB, after which AT III activity slowly increased. Eighty percent AT III activity returned on the second postoperative day, not immediately after protamine administration. There was no significant difference in AT III activities in the two groups (Fig. 1).

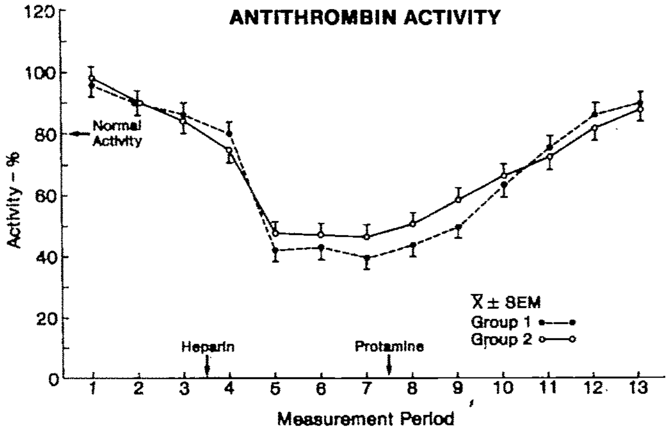

Figure 1. Antithrombin activity did not return to normal (> 80% activity) until the second postoperative day. The two groups were not statistically significantly different. See text for definition of measurement periods. Patients in group 1 were given protamine over 5 min, and those in group 2 received protamine over 30 min.

Discussion

Several relationships evolve from this study. First, heparin concentrations were slightly higher in group 1 after protamine administration. Second, the results of coagulation studies were significantly different 2 hr after protamine administration despite the fact that heparin concentrations were equal. Third, AT III activity did not return to preoperative levels immediately after protamine administration.

Overall, analysis of variance revealed no difference in heparin concentrations between the groups; however, an ANOVA evaluation of the data from measurements 8–10 showed that heparin concentration decreased significantly more slowly in group 1 than it did in group 2. This difference was small and assumes only minor clinical significance. One explanation for the difference in postreversal heparin concentration relates to sampling times. The first postreversal sample (sample 8) was drawn 15 min after completion of protamine administration. Blood samples in group 1, therefore, were drawn 25 min earlier in relation to spontaneous heparin clearance. We assume that this 25-min difference in sampling times is the major reason for the small difference in plasma heparin concentrations. Heparin rebound simultaneously occurring with protamine administration could retard disappearance of heparin from the circulation and further explain the slower decrease in heparin concentration in group 1. The cause of heparin rebound remains controversial, and many theories have been advanced to explain its occurrence (10–14). Heparin is taken up by reticuloendothelial cells (15). From this potential storage site, heparin can be released into the circulation to become active again. Heparin also is taken into endothelial cells and possibly metabolized (16,17). Whether pharmacologically active unmetabolized heparin is released from this site is unknown. Heparin rebound could also relate to protamine metabolism (18). Both bound and unbound protamine are metabolized in plasma at 37°C. Once protamine is metabolized, released heparin could become active again.

Heparin concentrations equalized 2 hr after protamine administration. However, coagulation profile drawn at measurement 10 revealed greater heparin activity in group 1. The greater residual heparin activity in group 1 in the presence of equal heparin concentrations remains perplexing and highlights the importance of clinically distinguishing heparin concentration and activity. Although we cannot rule out the possibility of disseminated intravascular coagulation or differential platelet activity in group 1, these explanations remain only remote possibilities by virtue of normal clinical clotting. Despite these laboratory findings, patients in group 1 neither lost nor received more blood than patients in group 2.

Antithrombin III activity decreased with initiation of cardiopulmonary bypass. This change was likely due to acute hemodilution. Antithrombin III activity slowly increased after protamine administration, not abruptly as suggested by Kitani et al. and Okajima et al. (6,7). Differences in experimental technique may explain this finding. Our technique measured enzyme activity, whereas other investigators measured protein concentrations. This second method does not measure anticoagulant activity of the protein. Because AT III activity remained below 80% for 24 hr after bypass, the patients are potentially at risk for formation of venous thrombi during the first postoperative day (19).

In summary, slowly administered protamine not only may circumvent its negative hemodynamic effects in patients with poor left ventricular function (5), but also, as this study reveals, it results in clinically acceptable coagulation with improved postoperative coagulation studies. Because blood loss was similar, rapid administration of protamine offers no advantage over slow administration of protamine. Interestingly, protamine does not restore AT III activity. This finding establishes the possibility of postoperative thrombus formation in a patient whose blood is clotting in the presence of reduced AT III activity and emphasizes the importance of preoperative antiplatelet therapy (20,21).

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ANESTH ANALG
1986;65:381–4

The Effects of Atracurium Besylate (Tracrium®) on Intracranial Pressure and Cerebral Perfusion Pressure

Giovanni Rosa, MD, Paolo Orfei, MD, Maria Sanfilippo, MD, Vincenzo Vilardi MD, and Alessandro Gasparetto, MD

ROSA G, ORFEI P, SANFILIPPO M, VILARDI V, GASPARETTO A. The effects of atracurium besylate (Tracrium®) on intracranial pressure and cerebral perfusion pressure. Anesth Analg 1986;65:381–4.

Twenty-five patients with expansive pathologic brain lesions, who were anesthetized with thiopental, nitrous oxide in oxygen, and fentanyl, and who were mechanically ventilated to ensure normocarbia, received atracurium besylate 0.6 mg/kg, intravenously. Intracranial pressure, mean arterial pressure, central venous pressure, heart rate, and end-tidal CO_2 *were simultaneously recorded for 5 min before and for 10 min after administration of the muscle relaxant. No statistically significant changes were observed after administration of atracurium besylate. These results suggest that atracurium besylate may be used for muscle relaxation during neurosurgical operations, despite its potential for histamine release and excitement of the central nervous system.*

Key Words: NEUROMUSCULAR RELAXANTS—atracurium.

Atracurium besylate is a novel bis-quaternary competitive neuromuscular blocking agent devoid of undesirable cardiovascular side effects (1). Its effect on cerebral metabolic rate ($CMRO_2$), cerebral blood flow (CBF), and intracranial pressure (ICP) has been studied in dogs by Lanier et al. (2). Haigh et al. (3) have studied its effect on intracranial and intraocular pressure in monkeys. This study evaluates the effects of high doses of atracurium on ICP and other cardiovascular variables in neurosurgical patients undergoing general anesthesia.

Methods

Twenty-five adult patients (19–62 yr of age) with cerebral tumors and papilledema undergoing neurosurgical operations under general anesthesia were included in this study (Table 1). All patients gave informed consent, and the study was approved by the Human Experimentation Review Committee of the Anesthesia and Resuscitation Department, University of Rome "La Sapienza."

Premedication consisted of atropine, 0.01 mg/kg, and phenobarbital, 1.5 mg/kg, given intramuscularly approximately 45 min before the operation. Anesthesia was induced with thiopental, 5 mg/kg, and maintained with 60% N_2O in O_2 and fentanyl, 0.01 $mg{\cdot}kg^{-1}{\cdot}hr^{-1}$. Tracheal intubation was performed after a bolus injection of succinylcholine, 1 mg/kg.

All patients were placed in the supine or lateral position with the head elevated 15° to facilitate venous drainage. All were mechanically ventilated to ensure normocarbia (Pa_{CO_2} 35.13 ± 3.14 mm Hg) and continuously monitored for ECG, heart rate (HR), end-expiratory CO_2, systemic arterial blood pressure (SABP), and central venous pressure (CVP). A Teflon cannula (18-gauge) was introduced into a radial artery for measurement of SABP and a Teflon catheter (14-gauge) was inserted via the right internal jugular or subclavian vein in order to measure CVP. Systemic arterial blood pressure and CVP were recorded from two Gould Statham P23 transducers and continously displayed on a Siemens Sirecust 404 modular monitoring system together with the end-expiratory CO_2 and ECG (Siemens system). Intracranial pressure was measured using an epidural pressure transducer (Gaeltec ITC/b) that was calibrated prior to insertion with zero checked in situ (4). This was inserted for a length of 3 cm via the first burrhole performed, and the output was amplified using the Gaeltec Amplifier 57/b.

At least 30 min after succinylcholine injection and when all the measured parameters were stable, atra-

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Address correspondence to Dr. Sanfilippo, Istituto di Anestesiologia e Rianimazione, Universitá "La Sapienza," Viale del Policlinico, 00161 Rome, Italy.

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Table 1. Patient Data

Patient number	Sex	Age (yr)	Intracranial pathology
1	M	54	Olfactory groove meningioma
2	M	19	Right frontal metastasis
3	F	61	Right occipital astrocytoma
4	M	51	Right frontal glioblastoma
5	M	38	Right parietal glioblastoma
6	F	62	Left frontal metastasis
7	M	58	Right tuberculum sellae meningioma
8	F	50	Left parietal meningioma
9	F	60	Right frontoparietal metastasis
10	M	36	Right parietooccipital cystic astrocytoma
11	M	49	Right temporal glioblastoma
12	F	61	Olfactory groove meningioma
13	F	34	Craniofaringioma
14	M	36	Left frontal astrocytoma
15	M	58	Right occipital glioblastoma
16	F	39	Right frontal astrocytoma
17	M	52	Right frontal basal metastasis
18	M	46	Left sphenoidal ridge meningioma
19	F	52	Parasagittal oligodendroglioma
20	F	46	Right temporal fossa meningioma
21	M	59	Right parietal astrocytoma
22	M	52	Frontal parasagittal meningioma
23	F	55	Right temporal glioblastoma
24	M	61	Right frontal metastasis
25	M	56	Right temporoparietal astrocytoma

curium, 0.6 mg/kg, was administered intravenously. The speed of the injection was over 60 sec in the first 16 patients and then progressively shortened to 5 sec.

End-expiratory CO_2, SABP, CVP, and ICP were registered continuously on a four-channel MFE 1400 polygraph recorder at a paper speed of 50 mm/min. Recording started 5 min before injection of muscle relaxant to obtain control baseline data and for 10 min afterwards.

The neurosurgical operation continued after the recording had ended. Mean values of SABP, CVP, ICP, and HR were displayed on the monitors during investigation. The values for cerebral perfusion pressure (CPP) were calculated by the usual formula: CPP = MAP − ICP, where MAP is the mean arterial pressure. Fisher's test for variance analysis was applied to evaluate the statistical significance of the parameters studied; $P \leq 0.05$ values were considered statistically significant.

Results

Results and statistical data are shown in Table 2. None of the measured parameters showed statistically significant variations. More specifically, the basal values of ICP were, in all except three cases, within normal limits, even though all the patients had papilledema at the time of preoperative examination and in no case did ICP increase after administration of atracurium. In a few patients, ICP showed a greater than average decrease (patients 6,10,14,17), but this was not always correlated to higher initial ICP values or to greater variations in the other parameters measured simultaneously.

Discussion

After administration of muscle relaxant to artifically ventilated patients, a mild to moderate reduction of ICP may be expected (5). This is related to the decrease in CVP and mean endothoracic pressure resulting from relaxation of the skeletal muscles. However, it is well known that muscle relaxants often have undesirable cardiovascular side effects, in general secondary to effects on sympathetic or parasympathetic nervous conduction or to histamine release (6,7).

In turn, these unwanted side effects may provoke an increase in ICP (8–10) or a decrease in CPP that, even if modest, may irretrievably worsen the ischemic damage to the cerebral parenchyma (5,11) in patients with expansive-type intracranial pathologies.

In fact, a transient though potentially dangerous increase in ICP has been observed in some patients treated with succinylcholine and with *d*-tubocurarine. The latter may produce a more marked decrease in CPP by simultaneously decreasing MAP. The increase of ICP after administration of succinylcholine has been attributed to the increase in intracranial blood volume resulting from muscular fasciculations (12–14) or, more recently, to a transient cerebral vasodilation or venoconstriction produced directly or indirectly by the drug itself (15,16). In the case of *d*-tubocurarine, the increase of ICP has mainly been attributed to the cerebral vasodilatory effect of the released histamine (8,9).

Atracurium has a negligible effect on sympathetic and parasympathetic nervous conduction at clinically used doses (17). It may, however, release histamine into the circulation (18,19), although in much lower quantities than *d*-tubocurarine (20,21). Some authors (20–22) consider that these amounts are sufficient to produce unwanted hemodynamic effects in some patients, such as arterial hypotension and tachycardia.

Furthermore, laudanosine, the main metabolite of atracurium, has long been known to have an excitatory effect on the central nervous system (23–25). It originates by Hoffman elimination (26) and also seems to be present as an impurity in the commercially available unopened ampules (27). Lanier, et al. (2) have shown that doses of atracurium of 1 mg/kg or more administered to dogs during light halothane anesthesia cause an electroencephalographic arousal re-

Table 2. Responses to Atracurium[a]

Time	HR (beats/min)			MAP (mm Hg)			CVP (mm Hg)			ICP (mm Hg)			CPP (mm Hg)		
(min)	0	5	10	0	5	10	0	5	10	0	5	10	0	5	10
Patient															
1	64	68	68	80	80	80	4	4	4	9	8	8	71	72	72
2	75	77	75	68	68	68	5	5	5	16	14	14	52	54	54
3	70	70	70	90	90	90	8	7	7	5	4	4	85	86	86
4	65	65	65	83	83	83	6	5	5	8	8	8	75	75	75
5	74	74	74	65	65	65	3	3	3	10	9	9	55	56	56
6	50	52	50	90	90	90	8	4	4	28	24	18	62	66	72
7	73	73	73	70	70	70	7	6	6	22	19	18	48	51	52
8	67	70	67	78	78	78	8	7	6	6	6	6	72	72	72
9	60	60	60	70	70	70	3	3	3	20	20	20	50	50	50
10	80	80	80	95	90	90	10	8	8	12	7	6	83	83	84
11	74	74	74	72	72	72	5	4	4	25	24	22	47	48	50
12	60	65	65	70	70	70	9	9	9	8	7	7	62	63	63
13	70	70	70	85	85	85	6	6	6	7	7	7	78	78	78
14	70	70	70	90	90	90	5	4	4	14	10	9	76	80	81
15	62	64	64	73	73	73	6	4	4	16	14	12	57	59	61
16	60	60	60	75	75	75	10	10	10	14	12	12	61	63	63
17	60	60	60	75	75	75	4	3	3	12	10	8	63	65	67
18	78	78	78	70	70	70	7	7	7	4	4	4	66	66	66
19	75	75	75	75	75	83	8	5	6	4	4	3	71	71	80
20	70	70	70	74	76	76	4	4	4	7	5	6	67	71	70
21	70	70	70	75	77	86	8	6	7	4	3	3	71	74	83
22	60	60	60	70	70	70	5	5	5	4	3	3	66	67	67
23	76	75	75	88	88	88	6	6	6	14	13	13	74	75	75
24	62	64	62	66	68	70	4	3	3	10	9	9	57	59	61
25	56	56	56	74	74	74	3	3	3	7	6	7	67	68	67
Mean	67.24	68.00	67.68	76.88	76.88	77.64	6.04	5.24	5.28	11.44	10.00	9.44	65.44	66.88	68.20
SEM	1.52	1.44	1.48	1.69	1.59	1.63	0.43	0.39	0.39	1.35	1.24	1.08	2.09	2.05	2.15
F		4.67	(ns)		1.84	(ns)		4.34	(ns)		16.93	(ns)		6.95	(ns)

[a] Values given before and 5 and 10 min after administration of atracurium, 0.6 mg/kg.

Abbreviations: SEM, standard error mean; ns, not significant; HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; ICP, intracranial pressure; CPP, cerebral perfusion pressure.

action that is not, however, accompanied by statistically significant variations in $CMRO_2$, CBF, or ICP.

In the present study we evaluated the effects of intravenous administration of 0.6 mg/kg of atracurium besylate on ICP and CPP, as well as on the more common cardiovascular parameters. This muscle relaxant was given to patients under general anesthesia at a point during neurosurgical operation when all the studied parameters were stable.

Intracranial pressure was measured via an epidural transducer because it was not feasible to obtain consent for intraventricular measurement from most of the patients. However, extradural pressure correlates quite well with intraventricular pressure within wide limits (28). We used transducers that could be inserted and removed easily and quickly through a normal craniotomy burrhole and that could be calibrated in situ (4).

In the first 16 patients, intravenous injection of atracurium was made very slowly over 60 sec, first because it has been shown that the speed of drug administration is a critical element in the probability of histamine release (29), and second because it has recently been demonstrated that slow injection of atracurium prevented the clinical effects of histamine release in patients treated with 0.6 mg/kg of muscle relaxant (30). In the subsequent ten patients, injection speed was gradually increased but no alteration in the evaluated parameters was observed.

Therefore, in accordance with the results obtained by Haigh et al. (3) and by Lanier et al. (2) in animals, administration of atracurium besylate did not produce significant variations in ICP, CPP or in the other parameters measured in this study.

The results suggest that atracurium may be used safely for neuroanesthesia and neurologic intensive care, despite its accepted potential for histamine release and excitement of the central nervous system. Further studies are needed in animals and in humans, in order to explore the effects of laudanosine on the central nervous system, that might accumulate during long surgical procedures.

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Comparison of Oral Controlled Release Morphine and Epidural Morphine in the Management of Postoperative Pain

Anne-Marie Banning, MD, Jes Frederik Schmidt, MD, Bent Chræmmer-Jørgensen, MD, and Allan Risbo, MD

BANNING A-M, SCHMIDT JF, CHRÆMMER-JØRGENSEN B, RISBO A. Comparison of oral controlled release morphine and epidural morphine in the management of postoperative pain. Anesth Analg 1986;65:385–8.

Oral controlled release morphine (CRM) was compared in a double-blind study with epidural morphine (EM) for postoperative pain relief in 20 patients undergoing knee arthrotomy under epidural anesthesia. Ten patients received 30 mg CRM orally and saline epidurally (CRM group), and ten patients received placebo tablets orally and 4 mg morphine epidurally (EM group), both at the time of skin incision and then every 8 hr for 48 hr during which patients evaluated pain intensity using a visual analog scale. Nine of the ten patients in the EM group had good relief of pain throughout the study period. Seven of the ten patients in the CRM group needed rescue analgesics within 6 hr of the initiation of the study ($P < 0.01$). We conclude that CRM is not suitable for the control of early postoperative pain, whereas epidural morphine is excellent.

Key Words: PAIN—postoperative. ANALGESICS—morphine.

Oral controlled release morphine (Contalgin®) has been recommended as a convenient postoperative analgesic (1). Because gastric emptying may often be delayed postoperatively, oral morphine might not be absorbed sufficiently from the gastrointestinal canal to provide reliable pain relief. We therefore compared controlled release morphine (CRM) with epidural morphine (EM), which is known to provide excellent postoperative analgesia unaffected by gastrointestinal motility (2).

Methods

Twenty otherwise healthy patients aged 22–58 yr undergoing knee arthrotomy were investigated. The study was approved by the Copenhagen County Human Investigation Committee, and informed consent was obtained from each patient.

All patients received intramuscular morphine (women, 7.5 mg; men, 10 mg) for premedication 1 hr before the expected time of surgery. Epidural anesthesia was given to all patients through a lumbar epidural catheter using 2% mepivacaine with epinephrine.

The patients were randomly divided into two groups. One group (CRM) received 30 mg CRM (Contalgin®) orally and 10 ml normal saline epidurally; the other group (EM) received placebo tablets orally and 4 mg morphine epidurally in 10 ml normal saline. In both groups the first administration of morphine and placebo was at the time of skin incision (time zero) with subsequent administrations every 8 hr for 48 hr. No additional medication was given.

If the patients experienced inadequate pain relief, they were told to ask for additional analgesics, and then 1 mg/kg meperidine was given intramuscularly as "rescue" medication. These patients were withdrawn from further assessment apart from measurements of plasma morphine levels in the first 8 hr.

At times 0, 1, 2, 3, 4, 6, 8 and 12 hr after the beginning of surgery, pain intensity, the level of sedation, and respiratory rate were recorded. Blood samples were drawn simultaneously from an indwelling peripheral venous catheter for the determination of free morphine concentrations in plasma. Pain intensity was evaluated by the patients using an undivided visual analog scale (VAS: 0–100 mm, where 0 signifies no pain and 100 signifies unbearable pain). The level of sedation was assessed by one of the investigators using a 4-point scale where 0 stands for fully awake, 1 for awakened by speech, 2 for awakened by a painful stimulus, and 3 for no reaction to pain. Respiratory

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Address correspondence to Dr. Banning, Department of Anesthesia, Glostrup Hospital, DK-2600 Glostrup, Denmark.

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Table 1. Demographic Data

	CRM group[a]	EM group[a]
Sex (male : female)	7:3	6:4
Age (yr)	37[b]	41[b]
Weight (kg)	75[b]	75[b]
Duration of surgery (min)	50[b]	43[b]
Morphine dosage, premedication (mg/kg)	0.10–0.16[c]	0.10–0.16[c]
Mepivacaine dosage (ml)	14–25[c]	15–26[c]

[a] CRM group received 30 mg controlled release morphine orally and saline epidurally; EM group received placebo tablets orally and 4 mg morphine epidurally.
[b] Median.
[c] Range.

frequency was counted over 1 min; arterial blood samples for measurements of blood gas tensions were drawn if respiratory rate decreased below 8 per minute. Concentrations of free morphine in plasma were measured using radioimmunoassay (3).

At the end of the study period patients were asked to assess the quality of pain relief for the postoperative period as a whole, using a 5-point scale (no relief, slight relief, moderate relief, good relief, or pain free). They were also asked if they would accept the same method for relief of postoperative pain again.

The results were evaluated statistically using Student's *t*-test for comparison of mean morphine concentrations, the Mann-Whitney test for comparison of VAS scores, and Fisher's exact test for comparison of pain relief as a whole. The level of statistical significance was $P < 0.05$.

Results

Demographic data are shown in Table 1. There were no statistically significant differences between groups in Table 1. In none of the patients did epidural anesthesia last more than 3 hours (pin prick) after the start of surgery.

In the EM group 9 of 10 patients had adequate relief of postoperative pain and did not require additional analgesics. This compared to 3 patients in the CRM group who had adequate pain relief ($P < 0.01$). In Figure 1 are shown VAS scores for each patient in the 2 groups and the time when rescue analgesics were given on request. In Table 2 median VAS scores are shown. There are statistically significantly higher VAS scores in the CRM group at 3 and 4 hours. After that time VAS scores in the CRM group are still higher without statistical significance ($n = 3$).

In the EM group 1 patient was given intramuscular meperidine, 75 mg, 4 hours after the start of surgery without any pain relief. This patient was relieved of pain only after repeated doses of buprenorphine.

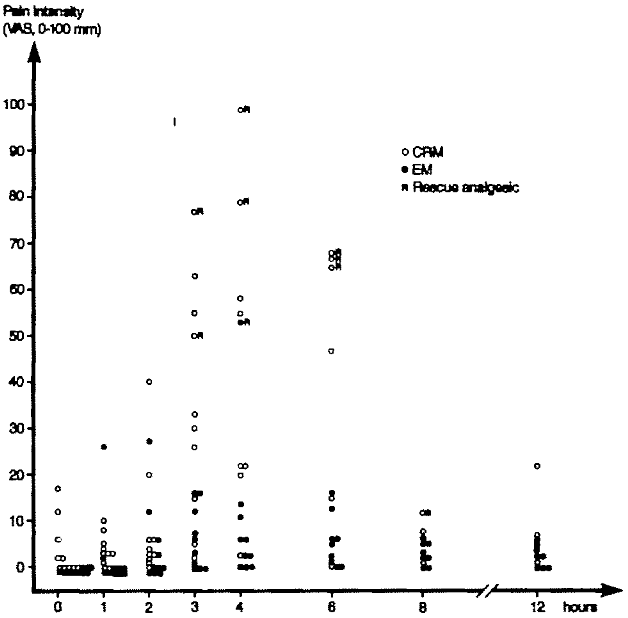

Figure 1. Pain intensity (visual analog scale scores) in relation to time in CRM (○) and EM (●) groups. R signifies administration of rescue analgesics.

Two hours after the beginning of surgery 1 patient in the CRM group required rescue analgesics. Altogether 7 patients in the CRM group required additional analgesics within 6 hours after the initiation of surgery. These patients had VAS scores above 50 at the time they asked for additional analgesics.

All patients had respiratory frequencies exceeding 10 breaths per minute during the study period. None of the patients had sedation scores above 1 (corresponding to awakened by speech).

Mean values of free plasma morphine concentrations are shown in Figure 2. Concentrations in the CRM group are slightly higher than in the EM group, but only at 6 hours is this difference statistically significant. Free plasma morphine concentrations did not exceed 20 ng/ml after the first dose of epidural morphine or Contalgin®. There was a steady decrease in morphine concentrations over the next few hours, very low values (0–5 ng/ml) being found after 8 and 12 hours. The correlation between VAS scores and plasma morphine concentrations is weak in both groups (CRM: $r = -0.27$; EM: $r = -0.18$).

Side effects were more frequent in the EM group with 4 patients nauseated and vomiting, 2 with universal itching and 1 developing urinary retention requiring bladder catheterization. In the CRM group 1 patient vomited. None of the patients found the side effects so severe that they wanted to withdraw from the study.

After 48 hours 3 patients in the CRM group were

Table 2. Median Values for Visual Analog Scale Scores after Start of Surgery

	Hours				
	3	4	6	8	12
EM group	4	4	6	4	3
(*n*)	(10)	(10)	(9)	(9)	(9)
CRM group	32	38	15	8	7
(*n*)	(10)	(8)	(3)	(3)	(3)
$P < 0.05$	yes	yes	no	no	no

See footnote to Table 1 for EM group and CRM group doses.

pain free or had good pain relief compared to 9 patients in the EM group ($P < 0.01$). The same 3 and 9 patients would accept the same method for relief of postoperative pain, should surgery be needed in the future.

Discussion

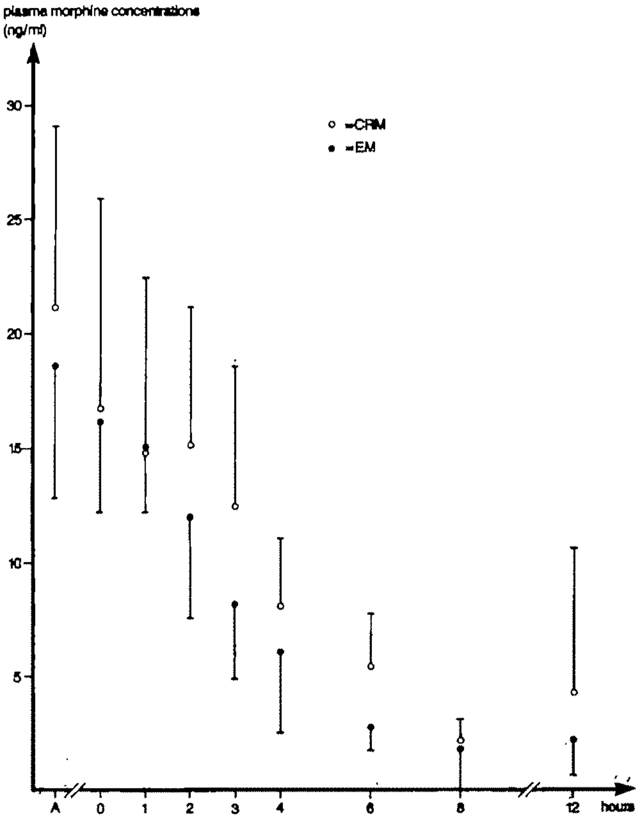

Figure 2. Plasma morphine concentrations in the CRM (○) and EM (●) groups. For the CRM group, $n = 9$, except at the 12-hr value where $n = 3$. For the EM group, $n = 9$. Mean values and standard deviations are shown. A signifies arrival in the operating room.

Controlled release morphine (CRM) has been recommended for the treatment of acute pain as well as cancer pain (1,4,5). Pharmacokinetic studies in human volunteers have shown that morphine concentration profiles after CRM differ significantly from those seen after conventional oral morphine. After CRM Leslie et al. (6), for example, found lower peak plasma free morphine concentrations but also morphine values at higher levels for prolonged periods. They suggested that the lower peak concentrations might possibly reduce side effects. Contradictory results have, however, been reported on the efficacy of CRM in providing relief of pain under clinical conditions. Fell et al. (1) compared pain relief with CRM administered on demand and relief with intramuscular morphine in an open study of 50 patients undergoing either hysterectomy or cholecystectomy. Doses in their study were CRM, 20–30 mg, orally approximately every 6 hours and intramuscular morphine, 10 mg/70 kg, approximately every 4 hours. Side effects were comparable in the 2 groups although patients receiving CRM were more sleepy. In a double blind trial of dental patients undergoing removal of impacted lower molars under general anesthesia, Hanks et al. (7) found, on the other hand, unsatisfactory pain relief after CRM 20 mg as well as after an oral aqueous solution of morphine sulphate 10 mg. Only 1 patient in their CRM group and 3 in the oral aqueous solution of morphine group had unequivocally good pain relief. Half the patients in each group needed an additional analgesic. Hanks et al. found no correlation between morphine concentrations in plasma and pain relief. Trying to explain why CRM is effective in the treatment of cancer pain but not acute pain, Hanks et al. suggested that morphine kinetics are altered with repeated doses so that the enterohepatic recirculation may contribute unconjugated morphine to plasma concentrations.

Epidural morphine, however, is known to produce excellent relief on post-operative pain. In a controlled clinical study Gustafson et al. (2) demonstrated good pain relief after knee arthrotomy for a period of approximately 12 hours, the effect being superior to and longer lasting than that of intramuscular morphine. Morphine concentrations in plasma were determined and peak concentrations were 20 ng/ml with epidural morphine (0.05 mg/kg) and 25 ng/ml with intramuscular morphine (0.1 mg/kg), respectively.

The present study was designed to evaluate the effect of oral CRM on acute postoperative pain. The above mentioned studies (1,2) suggested equipotency in terms of pain relief with CRM, 30 mg and EM, 4 mg.

In the present study intramuscular morphine was used for premedication. This complicates the interpretation of morphine plasma concentrations but serves the purpose of priming the patients with morphine.

From the plasma concentrations it should nevertheless be possible to detect whether or not oral morphine was absorbed. The pharmacokinetic studies of Leslie et al. (6) indicate that an increase in plasma morphine concentration would be expected approximately 4 hours after CRM ingestion. However, we found equally decreasing morphine values in the 2 groups, the concentrations measured at times 0–3 hours probably being derived from the intramuscular morphine given for premedication. Thus we could demonstrate no absorption of oral morphine.

In agreement with the results of Gustafson et al. (2) we found low plasma morphine concentrations after epidural morphine, confirming the theory that morphine applied extradurally does not enter the peripheral circulation on its way to the opiate receptors in the spinal cord (8).

In the present study epidural as well as oral morphine was given at the start of surgery when patients were totally pain free from epidural mepivacaine. We found insufficient relief of postoperative pain after CRM, 30 mg orally, in 7 of the 10 patients. Epidural morphine, however, provided excellent relief of postoperative pain. No obvious relationship between VAS scores and morphine concentrations was demonstrated. A vital question is whether or not doses were equivalent. Certainly they were not equivalent in terms of pain relief nor in terms of complications. However, from a theoretical point of view, we found it risky to increase the CRM dose further since gastric emptying postoperatively is unpredictable, and accumulated enteral morphine might later expose the patients to toxic doses.

The side effects found in this study following EM do not differ from those found in other investigations (9).

We conclude that controlled release morphine, 30 mg orally, cannot be recommended for the treatment of postoperative pain following knee arthrotomy. On the other hand epidural morphine, 4 mg every 8 hours, provides excellent relief of postoperative pain with, however, well known side effects.

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Cardiovascular Responses and Lidocaine Absorption in Fiberoptic-Assisted Awake Intubation

Anthony D. Sutherland, MBBS, FFARACS, and R. Tudor Williams, MRCS, LRCP, FRCP(C)

SUTHERLAND AD, WILLIAMS RT. Cardiovascular responses and lidocaine absorption in fiberoptic-assisted awake intubation. Anesth Analg 1986;65:389–91.

Local anesthetic toxicity and cardiovascular stress during fiberoptic-assisted awake tracheal intubation were assessed prospectively in 20 patients with airway management problems. Cardiovascular responses, dose of lidocaine, its systemic absorption, and patient comfort were measured. A standardized topical anesthesia protocol of 4% lidocaine aerosol, topical 2% lidocaine viscous gel, and direct perbronchoscopic laryngeal application was used. Awake intubation produced no significant elevation of blood pressure or pulse rate either during the topical application or after the intubation. Despite a large total dose of topical lidocaine (5.3 ± 2.1 mg/kg), the mean peak arterial plasma lidocaine concentration was low (0.6 ± 2.1 μg/ml). Patient comfort assessment showed that nine patients had no discomfort, whereas 11 had minimal discomfort. Supplementary sedation used was minimal (fentanyl, 1.4 ± 0.6 μg/kg, and diazepam, 1.9 ± 1.8 mg). This method of producing topical anesthesia for awake tracheal intubation is recommended as a safe, easy, and comfortable method of managing patients with airway difficulties.

Key Words: INTUBATION—tracheal. EQUIPMENT—fiberoptic bronchoscope.

Awake tracheal intubation is often the safest way to manage patients presenting for surgery with known or suspected difficult airways (1). Intubation using a fiberoptic bronchoscope (FOB) is becoming more common and is a major advance in airway management prior to induction of general anesthesia. Initially the nose was used as a logical guide to the larynx for fiberoptic bronchoscopy and subsequently for fiberoptic-assisted nasotracheal intubation. The nasal approach avoided potential damage to the FOB by the patient's teeth. Recently, a variety of oral airway obturators or guides have been described to enable easier and safer use of the fiberoptic bronchoscope through the mouth (2,3).

Local anesthetic toxicity and cardiovascular stress are well recognized patient hazards during awake tracheal intubation under topical anesthesia. Inhalation of nebulized lidocaine before the intravenous induction of general anesthesia has been shown to modify the cardiovascular response to standard laryngoscopy and tracheal intubation (4). The present prospective study was designed to evaluate the effectiveness and safety of a standardized technique of fiberoptic-assisted awake intubation. Dosage of topical lidocaine, systemic absorption of lidocaine, cardiovascular responses during the procedure, and patient comfort were measured.

Methods

Twenty adult patients with potentially difficult airways were prospectively studied. Informed consent and institutional approval of the study protocol was obtained. Potential airway problems included oral tumors, cervical spine deformity or instability, morbid obesity, and myopathies. Patients were premedicated with 150 mg oral ranitidine. Intravenous and intraarterial catheters were inserted using procaine for local infiltration anesthesia before starting application of upper respiratory tract topical anesthesia. Baseline blood pressure and pulse rate were recorded, and a control arterial blood sample for lidocaine analysis was taken. The patient was positioned on the operating table in a 35°, head up, flexed position.

Topical anesthesia was started using a standard nebulizer filled with 5 ml of 4% lidocaine and driven by a flow of 8 L of oxygen per minute. A 5-cm flexible connector from the nebulizer to a mouthpiece enabled easy positioning by the patient of the mouthpiece during inhalation of the lidocaine aerosol. After 2–3

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Address correspondence to Dr. Sutherland, Department of Anaesthesia, Foothills Hospital at the University of Calgary, Calgary, Alberta, Canada T2N2T9.

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Table 1. Patient Characteristics and Supplementary Sedation

Sex	ASA class	Age (yr)[a]	Weight (kg)[a]	Fentanyl (μg/kg)[a]	Diazepam (mg)[a]
Male, $n = 8$ Female, $n = 12$	I, $n = 5$ II, $n = 14$ III, $n = 1$	43 ± 17 (19–75)[b]	86 ± 28 (50–143)	1.4 ± 0.6 (0–2.5)	1.9 ± 1.8 (0–6)

[a]Mean ± SD. [b]Range indicated in parentheses.

Table 2. Cardiovascular Measurements during Awake Intubation[a].

Stage	Systolic blood pressure (mm Hg)	Pulse rate (beats/min)
Baseline	150 ± 17	83 ± 13
Airway insertion	148 ± 21	85 ± 16
Tracheal spray	153 ± 24	90 ± 16
Intubation	149 ± 21	94 ± 17
1 min	123 ± 20	86 ± 18
2 min	114 ± 18	83 ± 16
3 min	107 ± 13	83 ± 16

[a]Mean ± SD.

min of nebulization, the patient was given 5 ml of 2% viscous lidocaine gel to gargle for 1 min. Any residual gel was discarded. Further nebulization was continued for 3 min, and the nebulizer was then connected to a plastic oral airway intubator (Fig. 1).

Inhalation of the lidocaine aerosol continued via the airway intubator as it was slowly advanced into the oropharynx by the patient. After placement, the FOB was introduced through the intubator and the larynx visualized. Two milliliters of 2% lidocaine was injected through the FOB directly onto the vocal cords. If there was minimal patient response, the FOB was then passed through the larynx during a deep inspiration, a further 2 ml of 2% lidocaine was injected into the trachea, and the FOB was withdrawn. After lubrication of the bronchoscope with a water-soluble ointment, a size 7.0 cuffed endotracheal tube was ensleeved over the bronchoscope, which was reintroduced to a position of 2–3 cm above the main carina. The patient was instructed to take a deep inspiration, during which time the endotracheal tube was introduced into the trachea and a 2-mg/kg induction dose of thiopental was given slowly by an assistant. The position of the tip of the endotracheal tube above the main carina was confirmed visually as the FOB was withdrawn. The cuff was inflated, and general anesthesia maintained with nitrous oxide, oxygen, and isoflurane.

Intravenous fentanyl and diazepam were given in incremental doses by an assistant as required during the procedure, and the dosage was recorded. Cooperation and verbal contact with the patient were maintained at all times until after intubation.

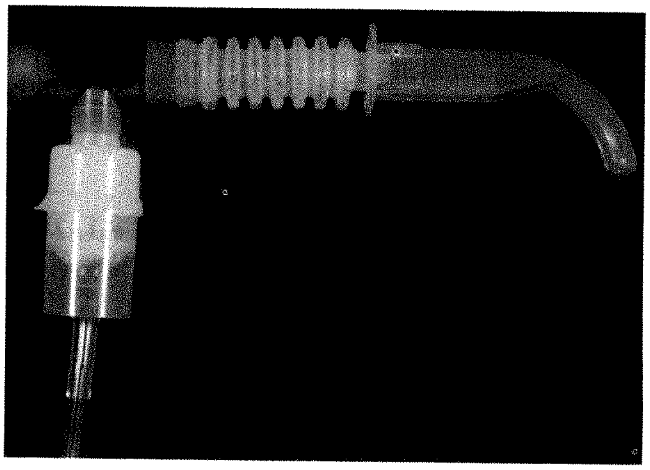

Figure 1. Airway intubator attached to oxygen driven nebulizer.

Blood pressure and pulse rate recordings were made by an independent observer at the following times: a baseline measurement before aerosol inhalation; after insertion of the airway intubator; after direct laryngeal and tracheal spray; after intubation; and at 1-, 2-, and 3-min intervals after intubation.

Arterial blood samples were also taken as follows: a control sample; after airway intubator insertion; before FOB insertion; after intubation; and at 5, 15, 25, 40, and 60 min after intubation The samples were analyzed for plasma lidocaine concentration using a polarized immunoassay technique. The normal therapeutic range for control of ventricular arrhythmias is 2–5 μg/ml plasma.

Patients were visited the day after surgery and were asked to select from a graded scale the degree of discomfort they remembered during the awake intubation procedure. The scale they were shown consisted of 0, no discomfort; 1, minimal discomfort; 2, uncomfortable; and 3, extremely uncomfortable.

Statistical analysis was performed using Student's *t*-test and linear regression analysis. Differences were considered significant if P values were less than 0.05.

Results

Awake intubation was successfully completed in all patients with minimal cardiovascular response, low systemic absorption of lidocaine, and high patient comfort. Supplementary sedation requirements during the procedure were low.

Patient characteristics, types of procedure, and doses

Table 3. Topical Lidocaine Dosage (mg)

	4% Aerosol	2% Viscous	2% Spray	Total dose	mg/kg dose
Mean ± SD	216 ± 44	109 ± 19	77 ± 22	403 ± 68	5.3 ± 2.1
Range	(120–320)	(80–160)	(40–120)	(300–540)	(2.5–11)

Table 4. Mean Plasma Lidocaine Concentrations at Seven Stages of the Procedure

Stage	Time (min)	Plasma lidocaine concentration (μg/ml, mean ± SD)
Airway insertion	10	0
Pre-FOB insertion	18	0.4 ± 0.3
Postintubation	23	0.5 ± 0.3
5 min	23	0.7 ± 0.4
15 min	33	0.6 ± 0.4
25 min	43	0.6 ± 0.4
40 min	58	0.6 ± 0.4
60 min	78	0.5 ± 0.3

of supplementary intravenous sedation are shown in Table 1. Mean systolic blood pressure and pulse rates during the procedure are shown in Table 2. The mean time from start of aerosol inhalation to tracheal intubation was 18 ± 4 min, with a range of 11–26 min.

Despite a high total dose of topical lidocaine (5.3 ± 2.1 mg), mean peak plasma concentration was low (0.6 ± 0.3 μg/ml), and the highest plasma concentration was 1.6 μg/ml (Table 3). Nine patients said they had no discomfort; 11 patients had minimal discomfort during the awake intubation. Fifteen patients could not recall the passage of the endotracheal tube.

The total dose of lidocaine administered and a total supplementary intravenous fentanyl dose of greater than 1 μg/kg ($n = 11$) both were found to correlate independently with a lower systolic blood pressure after intubation ($P < 0.05$). Plasma lidocaine concentrations showed no correlation with either the total dose or mg/kg dose of lidocaine administered or with the cardiovascular response to intubation (Table 4).

Discussion

Elective fiberoptic-assisted awake intubation is a well-tolerated and safe method of managing patients with difficult airways. Using the protocol described, minimal supplementary sedation was required, cardiovascular changes were minimal, systemic absorption of topical lidocaine was low, and patient comfort was high.

The awake fiberoptic technique offered specific advantages in the management of the following clinical situations. Three patients had unstable cervical spine lesions and had symptoms of nerve root pressure. Passive neck movements were avoided, and the patients were able to monitor their own nerve root symptoms. Neuromuscular blocking drugs were completely avoided in a young woman with myesthenia gravis presenting for thymectomy, thus simplifying her postoperative management.

The oral airway intubator provided bronchoscope protection and aided visualization of the larynx during fiberoptic intubation. The use of oral intubation avoided potential bleeding that may occur using the nasal route (2). A smaller than normal endotracheal tube was routinely used because some patients had distorted oropharyngeal and laryngeal anatomy. A size 7.0 tube was also a snug fit on the bronchoscope, minimizing any risk of the endotracheal tube catching on the larynx as it was passed over the bronchoscope. This is particularly important because the vocal cords in awake patients are active and not in the widely abducted position seen after administration of muscle relaxant drugs.

Awake intubation remains an important part of the skills of the clinical anesthetist. The described technique using the airway intubator and fiberoptic bronchoscope makes a previously difficult and uncomfortable procedure easier for both the patient and anesthetist. There was a wide safety margin for local anesthetic toxicity, and the predominantly patient-controlled inhalational mode of topical anesthesia aided patient acceptance and comfort. Although there was patient variation and a wide scatter of blood pressure and pulse recordings, overall changes in cardiovascular measurements were minimal, making the technique a useful alternative for patients presenting with difficult airways who have coexistent cardiac or neurologic disease.

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Neonatal Responses to Alphaprodine Administered during Labor

Kazusighe Murakawa, MD, Therese K. Abboud, MD, and Thormason Yanagi, MD

MURAKAWA K, ABBOUD TK, YANAGI T. Neonatal responses to alphaprodine administered during labor. Anesth Analg 1986;65:392–4.

The effect of intravenously administered alphaprodine on newborn Apgar scores, neonatal acid-base status, and the Neurologic and Adaptive Capacity Scoring System (NACS) were compared in 30 parturients. Patients in group 1 (n = 15) received 20–40 mg increments of alphaprodine, with a total dose of 39.3 ± 3.7 mg (X̄ ± SEM). Group 2 patients (n = 15) received no medication during labor. Apgar scores, neonatal acid–base status, and the NACS were equally good in the two groups. The concentrations of alphaprodine in maternal vein, umbilical vein, and umbilical artery at delivery were measured using a gas-chromatographic mass spectrophotometric technique. The results showed an umbilical vein-to-maternal vein ratio of 0.52 ± 0.09. It is concluded that when administered as in this study, alphaprodine has no adverse effects on the neonate.

Key Words: ANESTHESIA—obstetric. ANALGESICS—alphaprodine.

Alphaprodine (Nisentil), first described by Ziering and Lee in 1947 (1), has been used for the relief of labor pain for more than three decades. In 1953, Kane (2) reported the results of using alphaprodine subcutaneously in 1000 obstetrical cases. No maternal side effects other than transient dizziness in 0.8% of the cases were reported. Respiratory depression was observed in 4.9% of the neonates, and fetal mortality rate was reported to be 1.7%. The latter was not believed to be related to alphaprodine. Miller et al. (3) reported that statistically significant decreases in maternal tissue P_{O_2} and increases in tissue P_{CO_2} followed the intravenous administration of 0.4 mg/kg of alphaprodine during labor. There was also a significant decrease in baseline fetal heart rate and variability, though these changes were not associated with adverse maternal or gross neonatal effects. The extent of the more subtle neonatal effects of alphaprodine has not been fully evaluated.

The present study was undertaken to determine the effects of alphaprodine administered during labor on the mother, fetus, and neonate, as well as to measure its maternal and fetal plasma levels.

Methods and Materials

We studied 30 healthy parturients at term gestation. The study was approved by our Human Research Committee, and informed consent was obtained from all patients. All the patients had ruptured membranes and had direct electronic monitoring of the fetal heart rate. Uterine activity was evaluated by an intrauterine fluid-filled catheter connected to a pressure transducer.

Patients in group 1 (*n* = 15) received 20–40 mg increments of alphaprodine intravenously during the active phase of labor with a total dose of 39.3 ± 3.7 (X̄ ± SEM). Patients in group 2 (*n* = 15) did not receive any analgesics or medications during labor.

At the time of delivery, blood was drawn from a maternal vein and from the umbilical artery and vein of a doubly clamped segment of the umbilical cord for measurement of alphaprodine levels and acid–base status. All samples were put into heparinized vacutainers and put on ice. The plasma was removed after centrifugation and frozen until assayed for drug levels using a gas-chromatographic mass spectrophotometric technique, which will be reported in detail separately. The extraction procedure is similar to one previously reported for meperidine (4). The mass-to-charge ratios selected for single ion monitoring were *m/z* 172 for alphaprodine and *m/z* 114 for the internal standard, w-12174, a lidocaine analogue. The sensitivity of alphaprodine was 3 ng/ml. All neonates were evaluated by Apgar scores at 1 and 5 min, by umbilical venous and arterial blood acid–base status at the time of delivery, and by the Neurologic and Adaptive Capacity Scoring System (NACS) 15 min, 2 hr, and 24

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Address correspondence to Dr. Abboud, Department of Anesthesiology, Los Angeles County-University of Southern California Medical Center, 1200 North State Street, Los Angeles, CA 90033.

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Table 1. Patient Data[a]

	Alphaprodine	Control
Maternal age (yr)	21.9 ± 1.5	25.2 ± 1.5
Maternal height (cm)	153.0 ± 2.4	155.7 ± 2.3
Maternal weight (kg)	68.4 ± 3.1	67.3 ± 2.4
Parity		
Primiparous	8	6
Multiparous	7	9
Infant weight (g)	3594.0 ± 121.8	3486 ± 116
Gestational age (weeks)	39.8 ± 0.7	39.9 ± 0.4

[a] Mean ± SEM.
No significant differences between groups by Student's *t*-test.

Table 2. Acid–Base and Blood Gas Data

	Alphaprodine ($n = 15$)	Control ($n = 15$)
Umbilical vein		
pH	7.30 ± 0.02	7.33 ± 0.01
$\mathrm{Po_2}$ (torr)	25.2 ± 1.4	26.4 ± 0.9
$\mathrm{Pco_2}$ (torr)	34.0 ± 1.74	35.1 ± 1.1
Base excess (mEq/L)	−9.1 ± 1.2	−4.5 ± 1.2
Umbilical artery		
pH	7.24 ± 0.03	7.27 ± 0.02
$\mathrm{Po_2}$ (torr)	17.9 ± 0.8	18.8 ± 1.3
$\mathrm{Pco_2}$ (torr)	38.7 ± 3.3	44.3 ± 2.1
Base excess (mEq/L)	−9.1 ± 2.1	−5.4 ± 0.7

No significant differences between groups by Student's *t*-test.

hr after birth, according to previously described protocol (5). Apgar scores were assigned by pediatricians unaware of the analgesic management of the mother during labor. The NACS examination was performed by a trained anesthesia research fellow. The NACS gives a total score, the maximum being 40. Arbitrarily choosing 35–40 as the score denoting a vigorous baby (5,6), we determined the percentages of infants scoring 35 or higher and compared these between the study groups at 15 min, 2 hr, and 24 hr after birth. We also determined the percentage of infants having high scores on each of the individual test items. Data were analyzed for statistical significance using Student's *t*-test and χ^2-analysis when appropriate. A *P*-value of less than 0.05 was considered statistically significant.

Results

Data on maternal age, weight, height, parity, infant gestational age, and weight are summarized in Table 1. There were no significant differences between the two groups with regard to patient characteristics. All patients in the two groups had normal, spontaneous vaginal delivery. The interval between the last dose of alphaprodine and delivery was 197 ± 96 min ($\bar{X}$ ± SEM).

All neonates were vigorous at 5 min, and there was no significant difference in the incidence of low 1-min Apgar scores between the two groups. Four neonates in the alphaprodine group and three neonates in the control group had low 1-min Apgar scores. Umbilical artery and vein blood gases, pH, and acid–base status were within normal limits and did not differ significantly in the two groups (Table 2). The results of the NACS in the two groups of neonates are presented in Table 3. There were no significant differences between the two groups for any of the test items of the NACS with the exception of the habituation to light reflex, which was significantly higher in the alphaprodine group at 24 hr of age ($P < 0.01$). There were no significant differences for the percentage of infants who scored 35–40 on the NACS in the two groups.

Alphaprodine was detected in all maternal and fetal blood samples (Table 4), the fetal to maternal ratio averaging 0.52 ± 0.09 ($\bar{X}$ ± SEM).

Discussion

Narcotics such as alphaprodine and fentanyl with rapid onset and short duration of action seem to be the ideal narcotics for pain relief during labor. Theoretically, they can be given in advanced labor with less risk of subsequent neonatal respiratory depression than when longer acting narcotics are used. However, the respiratory depressant effect of alphaprodine is well-known (7) and appears to be dose-related. The reports in the literature of maternal respiratory arrest were associated with much larger doses of alphaprodine than those used in the present study. Miller et al. reported that 0.4 mg/kg intravenous alphaprodine given to mothers during labor (a dose similar to the dose we used in our study) significantly decreased baseline fetal heart rate and variability, decreased maternal tissue $\mathrm{Po_2}$, and increased maternal tissue $\mathrm{Pco_2}$. However, these changes were not associated with gross neonatal effects. In the present study we used the NACS examination, which has proved to be a sensitive test for detecting subtle neonatal drug effects (8–12), and found no adverse neonatal effects of alphaprodine. However, both in Miller's study and in the present study only healthy mothers with healthy fetuses were studied. The dose of alphaprodine was relatively small. Further work is needed to fully evaluate the neonatal effects of a large dose of alphaprodine in the compromised fetus with impaired uteroplacental blood flow.

Table 3. Percentage of Infants who Scored 2 for each Test Item of the Neurologic and Adaptive Capacity Score

	15 min		2 hr		24 hr	
	Alphaprodine[a]	Control[b]	Alphaprodine	Control	Alphaprodine	Control
Adaptive capacity						
1 Sound	60	67	93	93	96	100
2 Habituation to sound	60	33	67	73	80	46
3 Light	100	60	93	86	93	92
4 Habituation to light	60	36	47	60	93[c]	38[c]
5 Consolability	86	67	80	73	96	85
Passive tone						
6 Scarf sign	100	93	100	93	93	100
7 Elbow recoil	73	93	73	80	80	100
8 Lower limb recoil	93	86	86	93	93	92
9 Popliteal angle	100	93	93	86	93	92
Active tone						
10 Neck flexors	40	60	47	80	86	92
11 Neck extensors	53	67	53	73	86	100
12 Palmar traction	80	67	60	67	93	46
13 Supporting reaction	53	73	86	73	93	85
Primary reflexes						
14 Palmar grasp	80	86	73	93	80	92
15 Automatic walking	33	67	40	33	53	38
16 Sucking	80	80	93	80	100	100
17 Motor response	100	93	100	100	100	100
General assessment						
18 Alertness	80	100	86	100	100	100
19 Crying	86	86	73	86	100	100
20 Motor activity	73	93	66	93	86	92
Percent of good scores on all tests	66	60	60	80	93	92

[a] Group 1, $n = 15$.
[b] Group 2, $n = 15$.
[c] $P < 0.01$ using χ^2-test.

Table 4. Mean Maternal and Fetal Alphaprodine Plasma Concentrations (ng/ml)[a]

Maternal vein	60.8 ± 9.2 ($n = 9$)
Umbilical vein	31.0 ± 7.4 ($n = 9$)
Umbilical artery	34.8 ± 6.3 ($n = 6$)
Umbilical vein/maternal vein	0.52 ± 0.09 ($n = 9$)

[a] Mean ± SEM.

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Review Article

The Coronary Circulation and Myocardial Oxygenation in Coronary Artery Disease:

Effects of Anesthesia

Emerson A. Moffitt, MD, and Dhun H. Sethna, MD

The companion review to this article, published in last month's issue of *Anesthesia and Analgesia*, has already examined the coronary circulation, its anatomy and physiology, hemodynamics and regulation of normal coronary flow, along with alterations in hemodynamics due to coronary stenosis and metabolic indices of myocardial ischemia (52). In this review the patient with coronary arterial disease who must have anesthesia for a cardiac or noncardiac operation is considered. Because of the large number of patients having coronary artery bypass grafting (CABG) and the even larger number with coronary disease having other operations, anesthesiologists must deal with coronary patients regularly. Patients who have had a previous infarction have a higher risk of perioperative reinfarction and death than those without a known infarction (44,62,64). Thus a pertinent subject in anesthesia is how to manage the patient with coronary disease through anesthesia and recovery without incurring infarction. Paralleling the cardiac surgical advances of the last 15 years have been significant strides in the knowledge and clinical skill with which these patients are handled during anesthesia. Introduction of direct monitoring to anesthesia, particularly the pulmonary arterial catheter (63), plus the intravenous opiates (8,16,61) and new inhalational agents (5,7), have contributed to the ability to safely manage these patients through cardiac operations. Since the first reports in 1957–59 (6,9,13,19,27,40,42,43), publications too numerous to list have related hemodynamic studies during anesthesia for open-heart operations and added to the clinical knowledge for managing cardiac patients.

In the early days of open-heart surgery, the practice for anesthetizing children with congenital cardiac lesions was to keep the anesthetic state light so as not to depress the heart and circulation (43). More recently, for adults with coronary disease, the accepted philosophy and practice is to keep cardiac pumping function and blood pressure controllably depressed. That is, cardiac work and myocardial oxygen consumption (MV_{O_2}) should not be allowed to increase because the oxygen supply to myocardial ischemic areas may not increase sufficiently (20). In addition, responses of the autonomic nervous system allowing increases in heart rate and blood pressure must be attenuated. It is now accepted that low pressure–low demand anesthetic agents and techniques best allow preservation of myocardial oxygenation (17). Proof of this has emerged only since 1979 with application in the operating room of practical methods for measuring coronary blood flow and myocardial energy metabolism.

This review examines the current state of knowledge of coronary blood flow and myocardial oxygenation in humans with coronary lesions correlated with hemodynamics and cardiac function during and after anesthesia for CABG. The thesis stated above has been validated in patients with preserved ventricular function by myocardial energy metabolic studies during anesthesia with the commonly used agents. In addition to a review of the reports on humans by others, a series of studies by the senior author is presented. This series employs a standard protocol in

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Address correspondence to Dr. Moffitt, Department of Anesthesia, Victoria General Hospital, Halifax, Nova Scotia, Canada, B3H 2Y9.

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one class of coronary patient in order to investigate the action of anesthetic and cardioactive drugs. Similar information is not yet available from coronary patients with poor ventricular function. The review will not fully encompass the copious literature on anesthetic management of patients with ischemic heart disease.

Measurement of Coronary Blood Flow and Myocardial Oxygenation

Methods of measuring coronary blood flow for practical use in the operating room were not available until about 1970. From 1965 to 1972, Moffitt et al. studied myocardial energy metabolism in groups of patients during and after open-heart operations. Included were adults having aortic (32), mitral (29), and double valve (31) replacement; children with congenital lesions (30); and those developing fatal cardiogenic shock (26). The surgeon inserted a catheter into the coronary sinus (CS) after thoracotomy, allowing determination of arteriovenous differences of energy substrates intraoperatively and for 3 subsequent days. Left coronary flow could only be estimated during direct coronary perfusion when MVo_2 could be calculated. Effects of anesthetic drugs could not be investigated.

Although Rau (45) published in 1969 the argon method for determining coronary blood flow, its adaption to anesthetic research in humans was not reported until 1979 by Sonntag et al. (60). Similarly, although Ganz et al. (10) first reported in 1971 the thermodilution technique for measuring total coronary sinus blood flow (CSBF), use of this method in cardiac surgical studies began with Gray et al. (11) in 1977, Wilkinson et al. (67) in 1979, and Reiz et al. (46) in 1981. Because coronary disease is regional and not global, Baim et al. (1) introduced in 1980 a modification to the coronary sinus catheter by which both total coronary sinus flow and regional flow from the great cardiac vein can be measured.

Coronary blood flow normally varies with the need for myocardial oxygen (52). When measured over 30-sec intervals with the Ganz catheter before induction in 12 awake, sedated patients with Class III and IV disability, duplicate values for mean CSBF were 113.8 and 112.9 ml/min (24). However, wide ranges in measured coronary blood flow occur in patients with coronary artery disease. In one study mean arterial pressure (MAP) appeared to show a close correlation with coronary blood flow (34). Patients with the highest CSBF when awake (mean 176 ml/min, range 115–252) had an average MAP of 104 mm Hg (range 76–135), and patients with the lowest awake CSBF (mean 76 ml/min, range 62–96) had an average MAP of 78 mm Hg (range 74–101) (34).

Awake patients with NYHA Class III and IV disability breathing air (mean Pao_2 72 mm Hg) show a mean coronary sinus oxygen tension of 23 mm Hg (28). This results in a coronary venous oxygen saturation of 37%, which is the range regularly found in awake, sedated patients in the operating room. Calculated MVo_2 in such patients ranges from 9.9 to 10.2 ml/min (24,34,36). In contrast, in unpremedicated patients with an average MAP of 113 mm Hg and a mean heart rate of 75 beats/min, Reiz et al. found the mean MVo_2 to be 14.9 ml/min (48). During normal aerobic adenosine triphosphate (ATP) formation, 17% of arterial lactate is extracted by the myocardium (28). Finding more lactate in the coronary sinus than in the arterial blood (i.e., lactate production) indicates that efflux from anaerobic ATP formation exceeds influx in a large portion of left ventricular muscle. However, regional ischemia may not be reflected by either lactate sampling or flow measurement in the coronary sinus due to the dilution of metabolites with the much larger volume of blood-draining nonischemic muscle.

Study Methods and Patient Populations

Since 1979 Moffitt and associates have employed the Ganz catheter (10) to study CABG patients, using the same protocol with each individual or combination of agents investigated. Patients studied were as uniform as possible: candidates for CABG with ventricular function preserved (ejection fraction > 0.5), without ventricular aneurysm, heart failure, associated valve disease, hypertension, or pulmonary disease. Beta-adrenergic or calcium-blocking drugs were administered through the night before operation. In the operating room, a radial arterial cannula and two central catheters were inserted via the right internal jugular vein in sedated patients. One was the usual pulmonary artery (PA) thermodilution catheter (63), and the other was the CS catheter (10), the latter placed with the aid of fluoroscopy. Each series consisted of recording arterial and central pressures; measuring duplicate cardiac indexes (CI) and CSBF; ECG (V_5); and drawing arterial and CS blood samples for oxygen saturation, hemoglobin, and lactate content. Sequential series were done: awake, after induction, after intubation, before and after sternotomy, immediately after cardiopulmonary bypass, after chest closure, and 1 and 24 hr after the operation. Each study group consisted of 10 patients, except for those who received halothane or morphine (six patients).

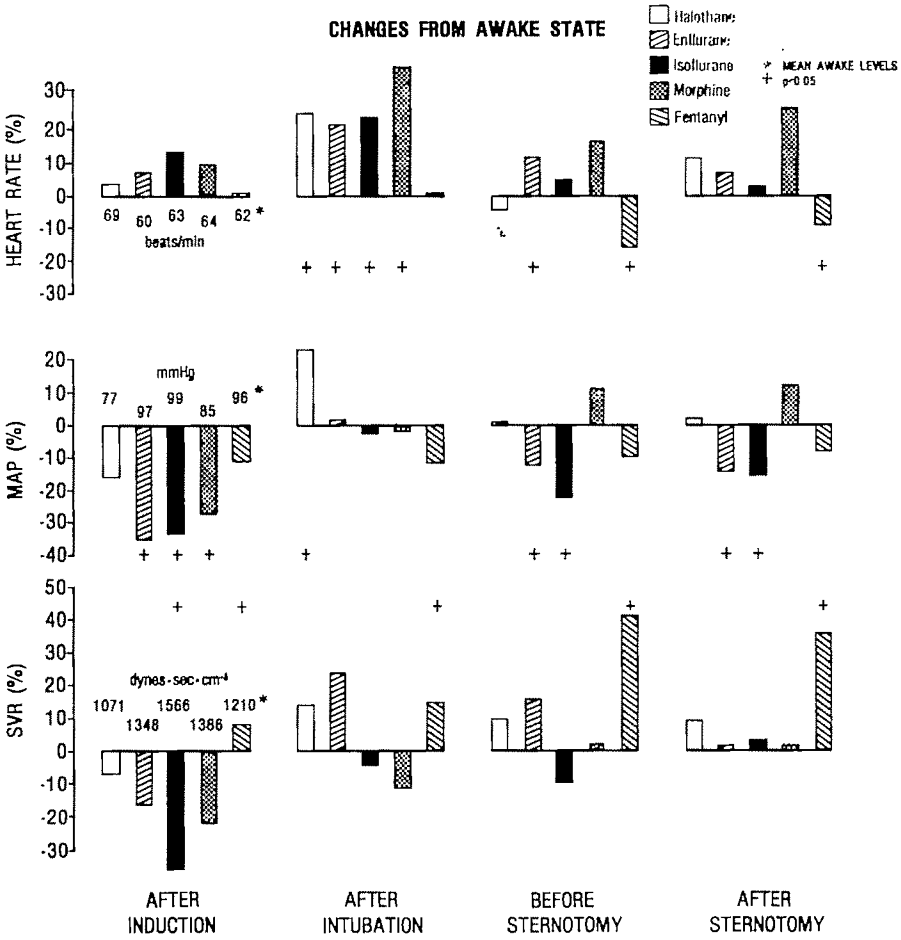

Figure 1. Percent changes from awake levels in heart rate, mean arterial pressure (MAP), and systemic vascular resistance (SVR) at four times before bypass with the five anesthetic drugs. Significant P values are identified by +.

Anesthetic protocols were standardized for each series. For induction, halothane (36) concentrations were given with oxygen, to reduce MAP by an average of 17% for 10 min before the second preintubation measurements. Enflurane (24) and isoflurane (23) were given similarly and decreased MAP 35 and 33%, respectively. The protocol was to decrease systolic blood pressure 25% from the preinduction value, although this was not achieved in the first study with halothane. Because blood pressure regularly decreases on induction, 25% was chosen as reasonable in this patient population. The expected reduction in myocardial oxygen usage during this manner of induction was documented in the first studies. Concentrations given during induction ranged from 0.93 to 3% (end-tidal) for enflurane, 0.67 to 3.8% for isoflurane, and up to 3% (inspired) for halothane. Pancuronium (0.1 mg/kg) was given slowly during induction. $Pa\text{CO}_2$ did not change during induction or throughout anesthesia, except during the bypass period. Anesthesia was maintained with concentrations necessary to keep systolic pressure slightly below awake values, i.e., to retain a steady, controlled hemodynamic depression.

Intravenous morphine (1 mg/kg) (36) was given over a mean of 17 min with oxygen inhalation before intubation; no additional anesthetic drugs were given during operation. Fentanyl (75 μg/kg) (34) was given intravenously for induction with oxygen inhalation, followed by an infusion of 10 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ until the end of cardiopulmonary bypass. For the nitrous oxide studies (33,39), 50% was added to oxygen 15 min after intubation for 15 min, to a background of 0.5% halothane, 0.5% enflurane, or the fentanyl anesthetic state. No stimulation was permitted during this time. For the two studies combining opiate and inhaled agent, induction began with fentanyl (30 μg/kg), followed by enflurane (18) or halothane (25) sufficient to reduce systolic pressure 25% for 10 min before intubation. Anesthesia was then maintained with the inhaled agent and oxygen, titrated to keep hemodynamics mildly depressed compared with the awake state. Hemodynamic calculations and metabolic determinations were by standard methods (36). Analyses of variance and Student's *t*-tests were performed to determine levels of significance, comparing subsequent series in each group to the awake state and measurements among groups when applicable.

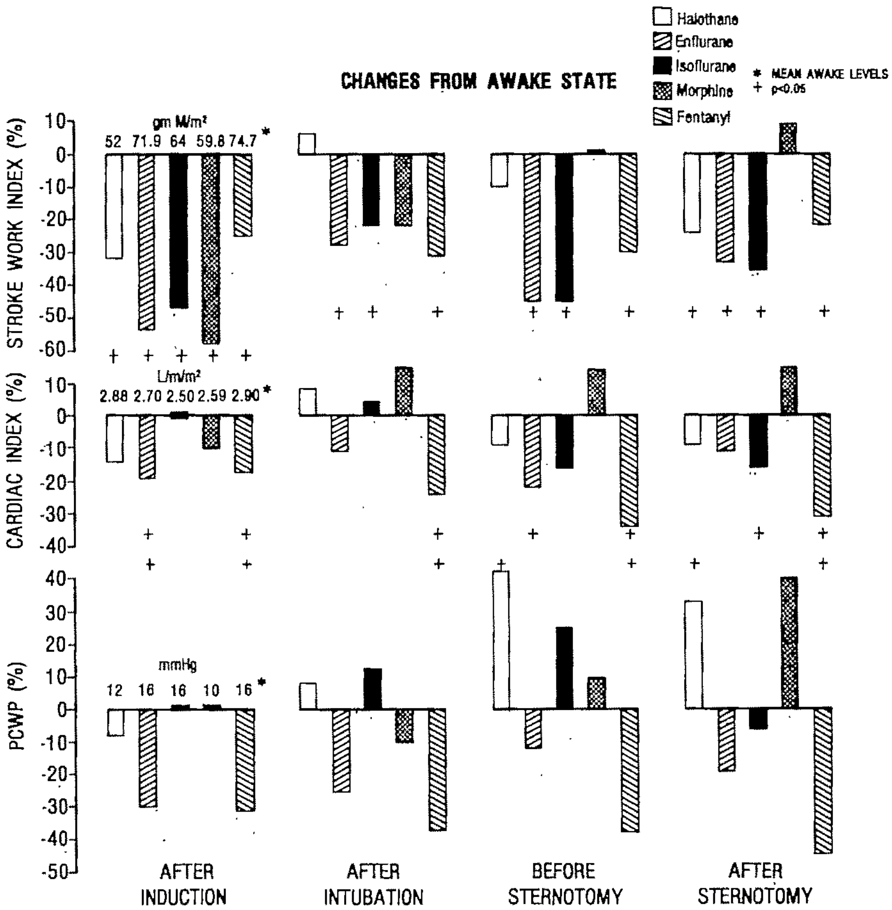

Figure 2. Percent changes from awake levels in stroke work, cardiac index, and pulmonary capillary wedge pressure (PCWP). Stroke work index decreased after induction with all agents and after sternotomy with all agents except morphine.

Coronary Blood Flow and Myocardial Oxygenation Correlated with Hemodynamic Function

Percent changes in mean values from the awake state for 12 hemodynamic and myocardial metabolic variables at four intervals before cardiopulmonary bypass are presented in Figures 1–4. Five groups of patients each received one of the major anesthetic drugs with oxygen for induction and maintenance. The inhaled agent was halothane (36), enflurane (24), or isoflurane (23), and the intravenous agent was morphine (36) or fentanyl (34). Mean values of variables in the awake, sedated patients are given, and statistically significant values identified.

Halothane

On induction MAP decreased (17%) without significant change in systemic vascular resistance (SVR), CI, or heart rate. Left ventricular stroke work index (SWI) was significantly depressed. The value of MVO_2 was reduced (34%) below baseline with the heart extracting less oxygen, resulting in significant increases in coronary sinus oxygen content (CSO_2). With intubation, MAP and heart rate increased above awake values, but myocardial oxygenation was not compromised (35), with no hearts producing lactate and no ST segment changes. Hemodynamics were not changed by sternotomy except for an increase in pulmonary capillary wedge (PCW) pressure, for which there is no apparent explanation. Myocardial oxygen supply i.e., CSBF, was unchanged throughout, and although CSO_2 increased and MVO_2 decreased after induction, they remained unchanged after intubation and sternotomy. Myocardial lactate extraction (MLE) continued in all six patients. Although hemodynamics were not kept as depressed before bypass in this early study as in subsequent studies with enflurane and isoflurane, MVO_2 remained at basal levels with no evidence of anaerobic metabolism.

Using the argon washin method for measuring CSBF, Sonntag et al. (60) found comparable results: halothane in healthy nonpremedicated subjects produced a dose-dependent reduction in CI and MAP; CSBF and MVO_2 decreased, probably because of deeper anesthesia than in our study; and MLE continued. Without using nitrous oxide, they gave an FI_{O_2} to

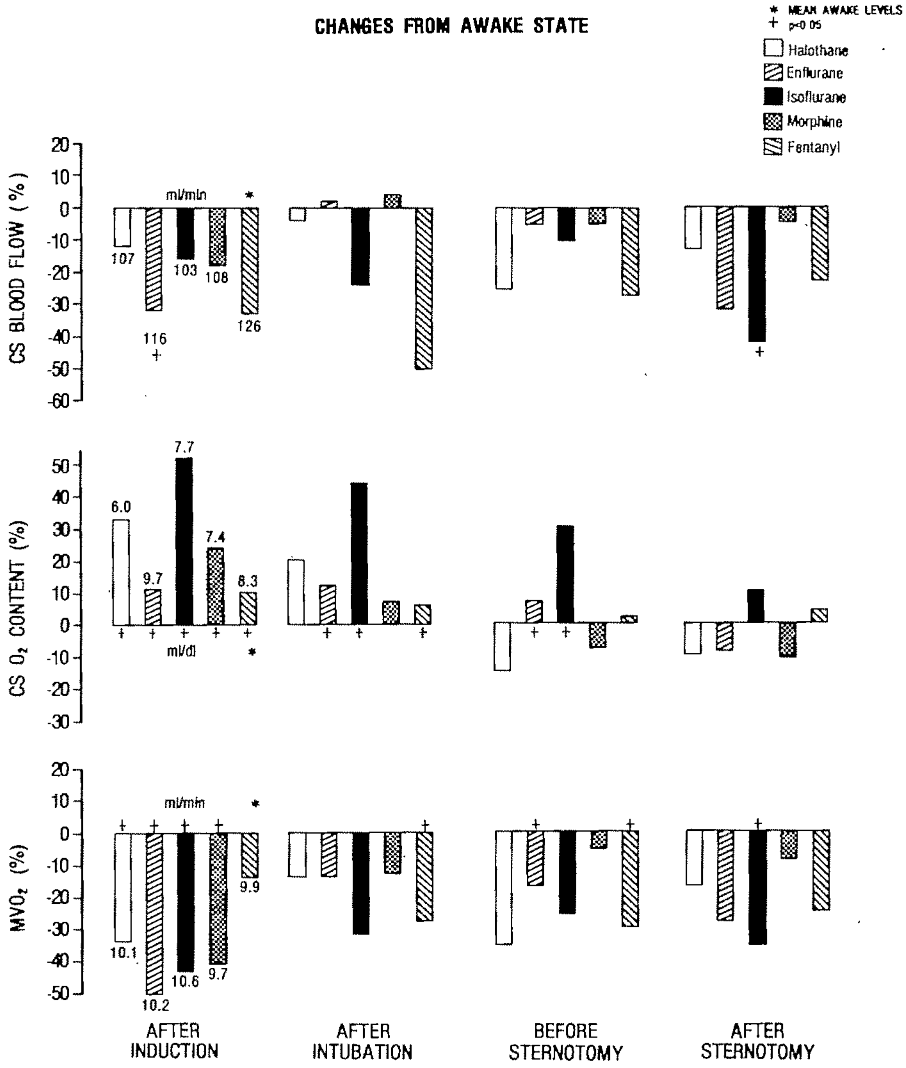

Figure 3. Percent changes from awake levels in myocardial oxygen consumption (MV_{O_2}), coronary sinus (CS) blood flow, and CS oxygen content. The greatest increase in CS_{O_2} content throughout was with isoflurane. Few changes in these variables were found from intubation on through sternotomy.

maintain Pa_{O_2} at 90 torr, unlike our FI_{O_2} of 1.0. Sonntag et al. (12) also reported on CABG patients given halothane (0.9% end-tidal) with 50% N_2O; no evidence of ischemia was documented. In contrast to these studies in patients with normal ventricular function, Reiz et al. (47) studied coronary patients in heart failure, who were having vascular operations employing the Ganz catheter (10). Halothane with 30% oxygen decreased CI, MAP, SVR, and SWI; CSBF decreased, as did MV_{O_2}; but no myocardial lactate production occurred. The authors suggested that halothane by systemic vasodilation unloaded the failing left ventricle, this effect being greater than the direct cardiodepressant action.

These studies show that metabolic control of coronary blood flow and MV_{O_2} is present during halothane anesthesia with maintenance of myocardial oxygen supply–demand relations, even after surgical stimulation.

Enflurane

The intentional reduction in MAP on induction occurred from myocardial depression (decreased CI) with reduced SWI without change in SVR. The decrease in CSBF (myocardial oxygen supply) was accompanied by a greater depression of myocardial oxygen demand (MV_{O_2}). Mean arterial pressure and SWI remained decreased at sternotomy, i.e., sympathetic responses to surgical stimulation were attenuated and MV_{O_2} was controlled. Neither arterial nor CS lactate increased at any time before cardiopulmonary bypass, and lactate extraction continued during and after anesthesia in every patient—the only group in which this occurred. Enflurane effectively dampened the circulation and MV_{O_2} throughout the study.

The protocol of Larsen et al. (15) involving enflurane differed from ours in that nitrous oxide was also given, which can have a major influence on the cir-

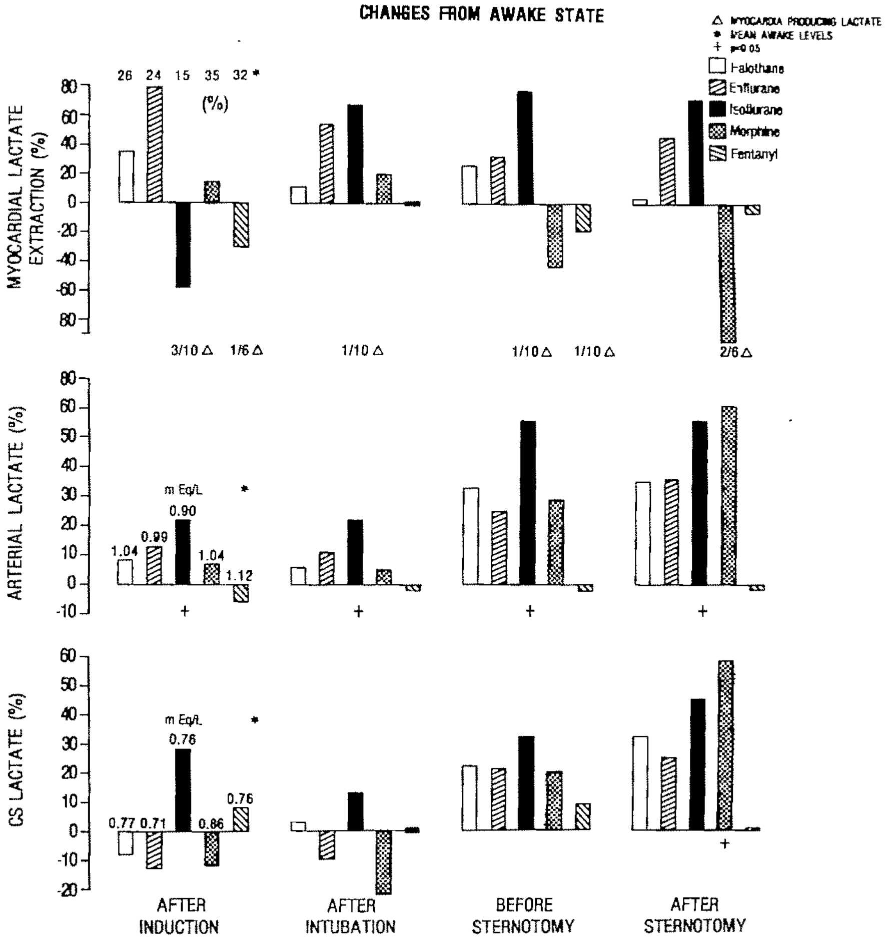

Figure 4. Percent changes from awake levels in myocardial lactate extraction and arterial and coronary sinus (CS) lactate concentrations, plus number of patients in whom myocardial lactate production was observed (△). Lactate production occurred more often with isoflurane than with other anesthetics, except after sternotomy, when morphine also was associated with myocardial lactate production.

culation (33,39). Mean arterial pressure and CI were reduced through sternotomy with no change in heart rate. Coronary sinus blood flow and MV_{O_2} remained depressed compared to baseline values, and no hearts produced lactate, i.e., no evidence of anaerobiosis. These studies show that enflurane also effectively maintained myocardial oxygen balance during anesthesia and surgical stimulation. Rydvall et al. (50) administered 70% nitrogen with enflurane (end-tidal 1.4%) for 30 min to non-β-blocked patients. This deeper anesthetic state (50% decrease in MAP), however, produced coronary dilation and myocardial ischemia in four of 11 patients.

Isoflurane

On induction MAP decreased due to a decrease in SVR, with no change in CI (23). With a 33% reduction in afterload and no change in heart rate or pulmonary wedge pressure (preload), one would expect an increase in CI (pumping function). That this did not occur suggests that isoflurane is a potent myocardial depressant, which is confirmed by the major depression of SWI. Systemic vascular resistance returned to awake levels on intubation and remained at this level. After sternotomy both CI and MAP were depressed with a major decrease in CSBF. Coronary sinus oxygen content (CS_{O_2}) increased on induction more than with any other agent and remained increased through sternotomy. Coronary vascular resistance (CVR) decreased significantly on induction, the only study in which this was seen. Despite this evidence of favorable oxygen balance, three of ten myocardia produced lactate after induction, one of which also did so after intubation. Another heart produced lactate before sternotomy. Of all studies by Moffitt et al., only in the isoflurane group was arterial lactate content elevated after induction, an increase continuing until bypass. Although isoflurane maintained a depressed circulation, regions of the myocardium were deficient in oxygen (lactate production) early during anesthesia, despite coronary vasodilation (elevated CS_{O_2}).

Similar results have been reported by others, despite differences in protocols. Reiz et al. (48) used the Ganz catheter in investigations of unpremedicated patients with coronary disease having aortic or iliac arterial operations. Induction included 70% nitrous oxide; subsequently "ventilation and $F_{I_{O_2}}$ were adjusted to maintain oxygen and carbon dioxide tensions at preanesthetic levels." With 1% isoflurane they documented decreased coronary perfusion pressure (35%) from systemic vasodilation and reduced cardiac performance. Coronary sinus blood flow did not change; thus CVR decreased 26%. Despite a decrease in MV_{O_2}, ST depression or T wave inversion developed in ten of 21 patients, suggesting regional ischemia. Because these ECG changes reverted on discontinuing the agent, ischemia presumably was due to reduced perfusing pressure, coronary flow redistribution (coronary steal), or both. The protocol of Reiz et al. (48) differed from ours in that our subjects were heavily premedicated, fully β-blocked, and received an $F_{I_{O_2}}$ of 1.0 during anesthesia. However, both studies documented myocardial ischemia. In an additional 13 patients with coronary disease, Reiz et al. studied 1.5 MAC isoflurane, given with 70% nitrous oxide for 45 min (49). Decreases in MAP (45%), SVR (40%), and CI (17%) were found. Coronary vascular resistance also decreased, and 7 patients had changes in ST segments. This study differed from that of Moffitt et al. (23) in its greater depth and duration of anesthesia and use of a lower $F_{I_{O_2}}$ plus nitrous oxide. Myocardial lactate production (ischemia) also occurred after sternotomy in three of ten patients studied by Larsen et al. (15) during isoflurane–nitrous oxide anesthesia. Mean arterial pressure and CI decreased along with MV_{O_2}, but CSBF returned to the awake level after sternotomy.

These studies show that isoflurane, when administered by the same investigators under similar experimental conditions as halothane and enflurane, is consistently associated with a higher incidence of regional myocardial ischemia.

Morphine

Although morphine is not now widely used as a major anesthetic agent, the effects of a 1 mg/kg dose are informative because of the positive findings (36). Mean arterial pressure decreased 27% despite a slow induction but returned to the awake level on intubation. This decrease in perfusion pressure resulted in an 18% reduction in coronary blood flow, but was associated with greater reduction in MV_{O_2} (40%) and increase in CS_{O_2} (25%). Morphine, like other anesthetics, decreased myocardial oxygen demand more than oxygen supply. At sternotomy, CI, MAP, and SWI were at awake levels with no reduction in CSBF and MV_{O_2}. Coronary sinus lactate content increased after sternotomy, and MLE decreased markedly, with two of six hearts showing lactate production (ischemia). This occurred without changes in ST segments on the ECG (V_5), indicating that absence of ECG changes may not be assurance of adequate myocardial oxygenation. The ischemia after sternotomy upon increase in heart rate in the absence of depression of CI and MAP contrasts with the absence of ischemia during intubation using halothane when MAP and heart rate increased but with no change in CI (36). One explanation for this difference may be that by the time of sternotomy, significant surgical stress was also present. Similarly Kistner et al. (14) noted that elevations in heart rate and blood pressure occurred frequently after sternotomy, accompanied by changes in ST segments in patients who received morphine (2.1 mg/kg) for induction. It appears that 1–2 mg/kg of intravenous morphine as the sole anesthetic is unable to effectively control autonomic stimulation or depress cardiac work and MV_{O_2} during surgical stimulation.

Fentanyl

In our β-blocked patients (mean propranolol dose 163 mg/day, heart rate 62 beats/min) given 75 μg/kg of fentanyl, no change in heart rate occurred after 0.1 mg/kg of pancuronium or after intubation (34). In fact the heart rate was decreased at sternotomy. Mean arterial pressure remained unchanged throughout, as decreased CI was countered by elevated SVR; PCW pressure and SWI remained below awake levels. Coronary sinus blood flow did not change before bypass, and elevated CS_{O_2} at induction lasted only through intubation. Fentanyl produced the least change in arterial and CS lactate content, but one myocardium showed lactate production after induction and one other before sternotomy without ECG changes. Although group hemodynamic responses were as shown (Figs. 1,2), two patients became hypertensive after the poststernotomy study and required vasodilation. Two others were removed from the study because they required continued vasodilation for hypertension, beginning before sternotomy. High-dose fentanyl with a maintenance infusion (total mean dose 109 μg/kg) did not dependably abolish autonomic stimulation. This inability to maintain a hypodynamic response to surgical stimulation in patients with good ventricular function has been reviewed by others and is similar to the experiences with morphine.

Skourtis et al. (58) reported on ten CABG patients studied with the Baim coronary sinus catheter (1). Using "high-dose fentanyl" of unstated dose with oxygen, they saw no change in CI, CSBF, heart rate, or MV_{O_2}. Systemic arterial pressure decreased after intubation but returned to awake level after sternotomy as SVR increased. Although CSo_2 decreased at both these times, they found no change in lactate extraction. In contrast, Sonntag et al. (59) gave high doses of fentanyl (mean total 127 μg/kg) to nine patients for CABG and found incomplete anesthesia and myocardial ischemia. Mean arterial pressure decreased with fentanyl, but it rose to awake levels without change in CI on sternotomy; CSBF and MVo_2 increased substantially after sternotomy, with seven of nine hearts producing lactate. Heart rate increased from 76 to 98 beats/min after sternotomy, suggesting incomplete β-blockade and insufficient depth of anesthesia. Compared with these findings, the relative absence of anaerobic glycolysis with fentanyl found by Moffitt et al. (34) may have been due to heavier premedication and complete β-adrenergic blockade. Moffitt et al. also gave a large dose of fentanyl (75 μg/kg) for induction before autonomic stimulation with a continued infusion, whereas Sonntag et al. intubated after only 10 μg/kg, and then administered the larger dose.

A recent conclusion of Thomson and Putnins (65) was that pancuronium is contraindicated for induction when given with fentanyl (50 μg/kg). They found that heart rate increased from 58 to 76 beats/min, rate–pressure product (RPP) also increased, and three of 12 patients developed ST segment depression. None of these occurred when metocurine or a metocurine–pancuronium mixture was given. Moffitt et al. have not seen either ischemia, as evidenced by ST change or by lactate production, or increases in heart rate or RPP when pancuronium (0.1 mg/kg) was given during induction in divided doses with 30 or 75 μg/kg fentanyl (see all figures). The lack of change in heart rate probably was due to a greater degree of β-blockade.

Nitrous Oxide

When a 50% concentration of nitrous oxide was added to anesthesia with halothane (39), enflurane, or fentanyl (33) in unstimulated CABG patients, hemodynamic depression occurred. Mean arterial pressure decreased, as did heart rate, CI, SVR, and CSBF. Mean lactate extraction diminished because CS lactate content increased without change in arterial lactate levels. With nitrous oxide added to halothane and to enflurane, these myocardia extracted more oxygen than without nitrous oxide, although one would expect less oxygen extraction with decreases in factors responsible for MVo_2, e.g., heart rate, CI, MAP. At the same time, CS lactate content increased, suggesting anaerobic glycolysis distal to stenoses. This occurred without ECG signs of ischemia.

Wilkinson et al. (66) reported on 26 CABG patients anesthetized with 50% nitrous oxide and halothane or morphine (2 mg/kg), studied with the Ganz CS catheter (10). They found elevated MAP, SVR, and CI after sternotomy with morphine–N_2O but not with halothane–N_2O. Ten of 14 halothane–N_2O and four of 12 morphine–N_2O patients showed ST segment depression or lactate production before cardiopulmonary bypass. This higher incidence of ischemia in halothane patients compared with our series may have been due to the presence of nitrous oxide. In contrast, patients anesthetized by Hilfiker et al. (12) with halothane–nitrous oxide showed a favorable myocardial oxygen balance.

Fentanyl–Enflurane and Fentanyl–Halothane Combinations

Induction began with fentanyl (30 μg/kg) followed by enflurane (18) or halothane (25) to produce a 25% decrease in systolic pressure before intubation. The inhaled agent was then continued as necessary to maintain a steady controlled depression of blood pressure. Percentage of change in mean values from awake levels for these two studies in the same 12 hemodynamic and energy metabolic variables are depicted in Figures 5–8.

The results with both combinations were so remarkably similar that they can be commented upon together. In fully β-blocked patients, neither intubation nor sternotomy changed heart rate. Mean arterial pressure was intentionally decreased (27%) on induction; neither intubation nor sternotomy increased MAP above the awake level. Systemic vascular resistance remained unchanged except for an increase with fentanyl–enflurane at sternotomy. Steady decrease of CI from awake level accounted for the lowered MAP, and PCW pressure showed essentially no change. With SWI consistently reduced, CSo_2 showed a large increase on induction and then gradually returned toward awake level before bypass. Coronary sinus blood flow decreased both after intubation and sternotomy, which also contributed to the consistent reduction in calculated MVo_2. Arterial and CS lactate increased before sternotomy; MLE for the group remained unchanged with one instance of lactate production after induction (fentanyl–enflurane) and one after intubation (fentanyl–halothane)

Postoperative hypertension requiring vasodilators occurred in two patients after enflurane and in three after halothane, in contrast to virtually all patients becoming hypertensive after halothane or enflurane anesthesia. With heart rate kept at awake levels and MAP below normal by judicious use of the inhaled

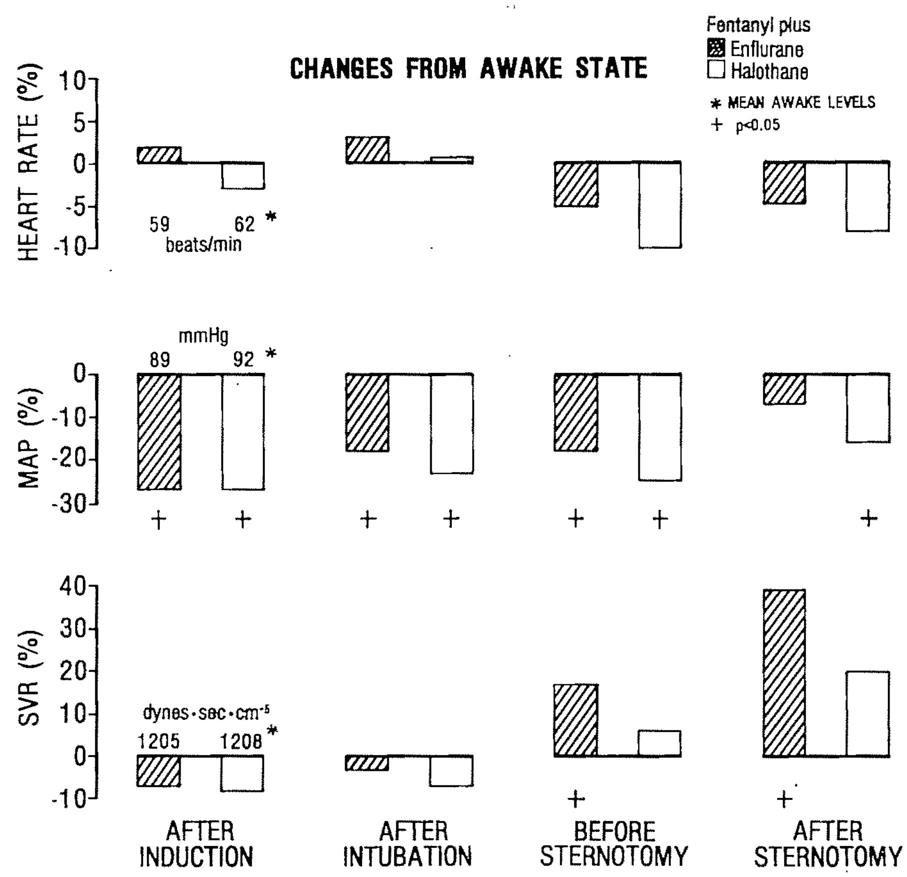

Figure 5. Percent changes from awake levels in heart rate, mean arterial pressure (MAP), and systemic vascular resistance (SVR) at four times before bypass during fentanyl–enflurane or fentanyl–halothane anesthesia (ten patients each). With no change in heart rate, MAP remained depressed. SVR increased only with fentanyl–enflurane after sternotomy. Significant differences are indicated by +.

agent, myocardial oxygen balance was also preserved, and essentially no anaerobic metabolism occurred before cardiopulmonary bypass.

Coronary Blood Flow and Myocardial Oxygenation with Cardiac Drugs

A variety of drugs with actions specific for the heart and circulation are regularly given during cardiac anesthesia. Although each is used for a necessary purpose, their effects on myocardial oxygen balance need consideration. Drugs of several classes have been investigated.

β-Adrenergic Blocking Agent—Propranolol

Are the effects of depressing cardiac output and heart rate detrimental when added to potent anesthetic agents? Propranolol (0.1 mg/kg) was given intravenously 45 min before induction to eight patients not previously β-blocked (22). No adverse hemodynamic effects were seen from the drug or from subsequent induction of anesthesia (morphine 1 mg/kg), compared with another group not given similar acute pretreatment (36). Sternotomy increased SVR but not heart rate or lactate extraction. The patients who were not pretreated with propranolol, but who received the same anesthetic regimen, had increases in MAP and heart rate after sternotomy, with two of six hearts producing lactate (36). Acute β-blockade aided in avoiding ischemia after surgical stimulation without additional depression of pump function during morphine anesthesia.

Positive Inotropic Agents

In accomplishing the needed increase in pumping performance, does myocardial oxygen supply keep up with the increased need?

Calcium chloride. Three hours after CABG, nine patients with low cardiac output had 1 g of intravenous $CaCl_2$ administered over 15 min (21). Cardiac index increased (1.76 → 1.99 $L \cdot min^{-1} \cdot m^{-2}$) as did MAP (77 → 94 mm Hg), but no changes were seen in heart rate, SVR, CSBF, MVo_2, or lactate extraction. After myocardial revascularization, calcium chloride given slowly at this dose produced hemodynamic improvement without unbalancing myocardial oxygenation.

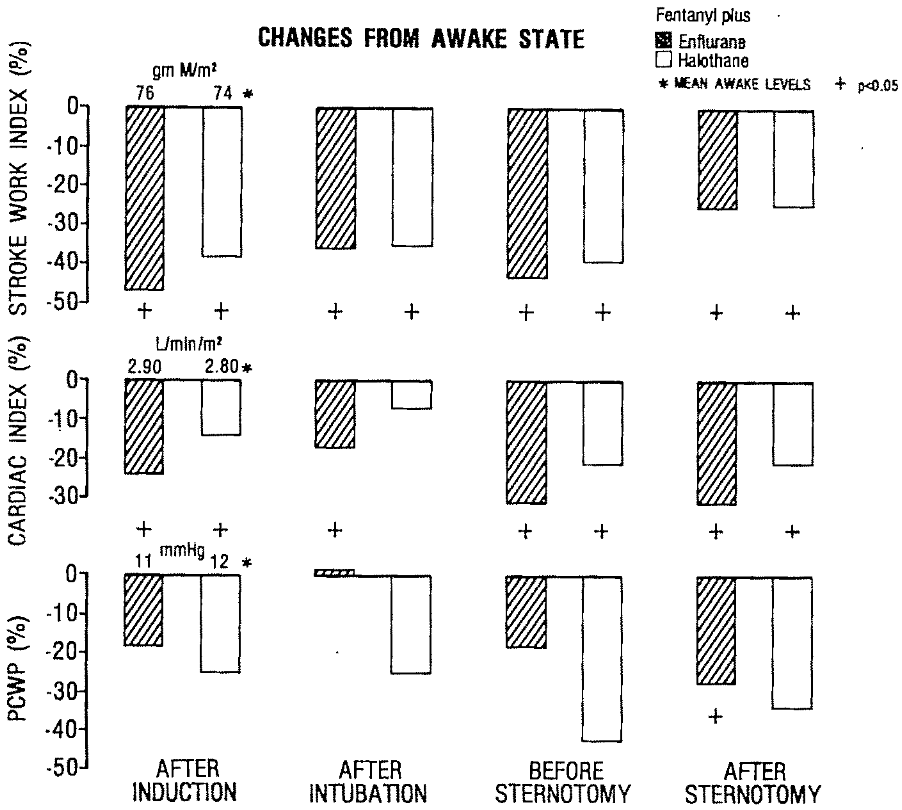

Figure 6. Percent changes from awake levels in pulmonary capillary wedge pressure (PCWP), cardiac index, and stroke work index during anesthesia with fentanyl plus enflurane or halothane. The lower MAP seen in Figure 5 was with decreases in cardiac index and no changes in PCWP. Stroke work index remained significantly reduced throughout.

Dobutamine. An infusion of dobutamine (mean 5.1 ± 2.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was given to seven patients shortly after CABG for an average of 26 min (51). Cardiac index increased (1.64 → 2.29 $L \cdot min^{-1} \cdot m^{-2}$) with heart rate increasing (70 → 87 beats/min). Mean arterial pressure was unchanged (85 → 90 mm Hg), whereas SVR decreased (2141 → 1708 $dynes \cdot sec \cdot cm^{-5}$). Coronary sinus blood flow increased (101 → 136 ml/min) as did MVO_2 (8.2 → 10.6 ml/min) without change in MLE. Oxygen consumption was elevated as cardiac work became greater, but no evidence of ischemia was found.

Digoxin. The myocardial metabolic cost of 0.5 mg intravenous digoxin was studied 1 day after CABG in seven patients who were progressing well (CI 3.17 ± 0.3 $L \cdot min^{-1} \cdot m^{-2}$, MAP 89 ± 10 mm Hg, heart rate 85 ± 10 beats/min) (57). No changes occurred in hemodynamics or CSBF. Myocardial oxygen consumption increased (7.2 → 8.7 ml/min), but normal MLE continued. This partial digitalizing dose had no adverse effects on myocardial oxygenation.

Vasodilating Drugs

When arterial pressure is reduced along with other hemodynamic effects, are cardiac work and MVO_2 similarly benefited?

Nitroglycerin. In one study (53) eight patients were given nitroglycerin (mean 2.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) infused for 6 min after sternotomy. Systemic vascular resistance decreased (1931 → 1090 $dynes \cdot sec \cdot cm^{-5}$) as did MAP (106 → 72 mm Hg), with no change in heart rate or CI. MVO_2 decreased (10.8 → 6.9 ml/min) as CSO_2 content increased (6.3 → 7.7 ml%) with no change in CSBF, i.e., reduction in blood pressure was accompanied by a decrease in O_2 consumption. In another study (38), seven patients, hypertensive both before induction and after sternotomy, had nitroglycerin infusions: mean 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ when awake and 1.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during anesthesia. In the awake state, only a small MAP decrease occurred (108 → 100 mm Hg), with reduction in CI (2.89 → 2.45 $L \cdot min^{-1} \cdot m^{-2}$), SWI (76.5 → 54.7 $g \cdot m \cdot m^2$), and PCW pressure (14 → 10 mm Hg). Heart rate increased (67 → 75 beats/min), as did SVR (1451 → 1613 $dynes \cdot sec \cdot cm^{-5}$); MVO_2 and MLE were unchanged. During anesthesia MAP decreased to normal (106 → 73 mm Hg), due to decreases in SVR (1931 → 1168 $dynes \cdot sec \cdot cm^{-5}$) and in PCW pressure (21 → 12 mm Hg). MVO_2 decreased (8.7 → 5.7 ml/min), as CSO_2 content increased (6.3 → 7.4 ml/dl); normal MLE continued. Nitroglycerin was more effective during anesthesia in returning the circulation to normal with beneficial reduction in myocardial oxygen need.

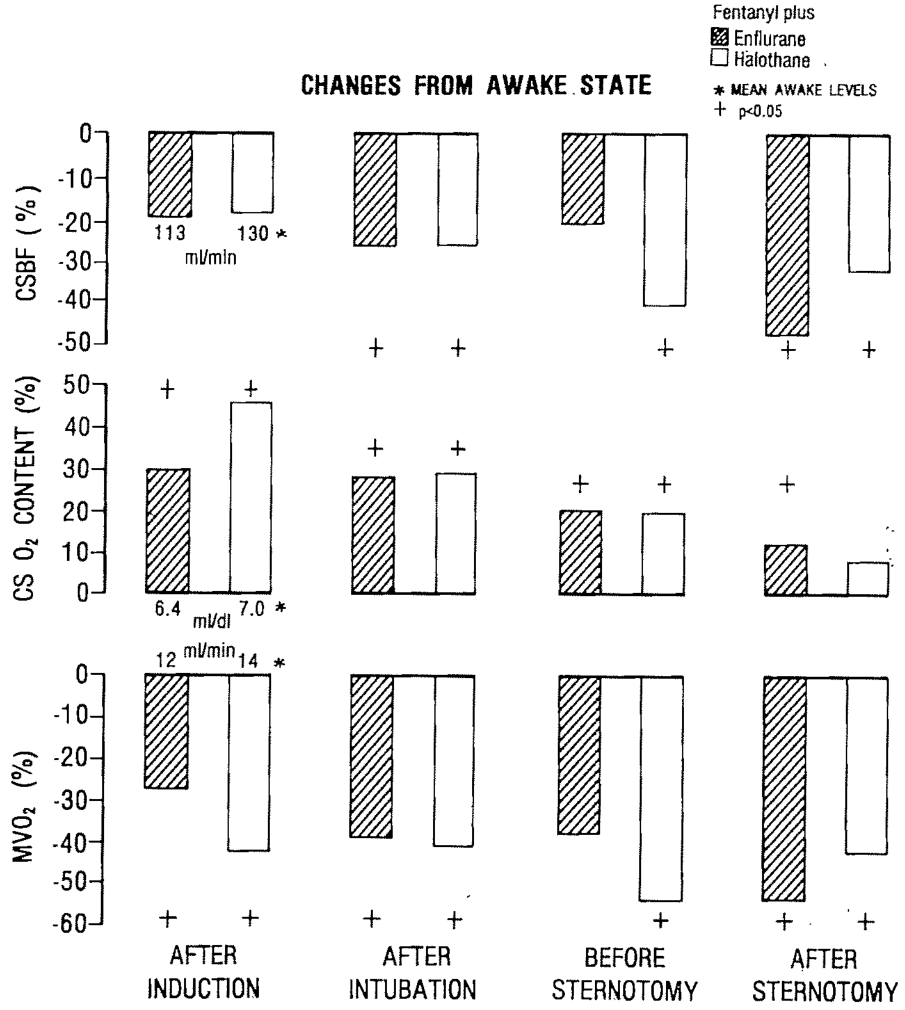

Figure 7. Percent changes from awake levels in coronary sinus blood flow (CSBF), coronary sinus O_2 content (CS_{O_2}), and myocardial oxygen consumption (MV_{O_2}) during anesthesia with fentanyl plus enflurane or halothane. MV_{O_2} remained significantly reduced as CSBF decreased and CS_{O_2} content increased.

Nitroprusside. Nine CABG patients received an infusion (mean 1.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in their first hour in the intensive care unit (4). Mean arterial pressure decreased (113 → 85 mm Hg), as did SVR (2397 → 1574 $dynes \cdot sec \cdot cm^{-5}$) without alteration in heart rate, CI, or CSBF. MV_{O_2} and MLE also showed no change. Nitroprusside decreased blood pressure from systemic vascular dilation in patients awaking from enflurane anesthesia, but oxygen consumption by the heart was not diminished.

Morphine. Effects of morphine, mean intravenous dose of 18.6 mg, were investigated in 11 CABG patients before induction of anesthesia (54). As SVR decreased (1383 → 1133 $dynes \cdot sec \cdot cm^{-5}$) so did MAP (100 → 84 mm Hg) with no change in CI or heart rate. Coronary vascular resistance decreased (0.85 → 0.70 $dynes \cdot sec \cdot cm^{-5}$); thus CS_{O_2} content increased (5.6 → 7.0 ml/dl) with no change in CSBF. This commonly given dose of morphine had a beneficial effect on arterial pressure and myocardial oxygenation.

Drugs Affecting Coagulation

Protamine sulfate typifies an agent necessary for another reason (antiheparin) that has potential detrimental cardiovascular effects. Nine CABG patients with good ventricular function were studied immediately after cardiopulmonary bypass (55), before drug administration, and 10 min after administration of protamine (mean 2.5 mg/kg in 3–6 min). No adverse hemodynamic effects were seen in these stable patients (MAP 84 → 82 mm Hg, CI 2.25 → 2.06 $L \cdot min^{-1} \cdot m^{-2}$, SVR 1438 → 1597 $dynes \cdot sec \cdot cm^{-5}$). There were no alterations in CSBF, MV_{O_2}, or MLE. The same study was also done in 11 patients who needed positive inotropic or vasopressor therapy during termination of bypass (56), i.e., who had been less stable hemodynamically. From the same circulatory state before protamine as the first group, the same protamine dose caused a significant fall in CI (2.35 → 2.04 $L \cdot min^{-1} \cdot m^{-2}$), whereas all other variables, including myocardial oxygenation, were unaffected. Protamine

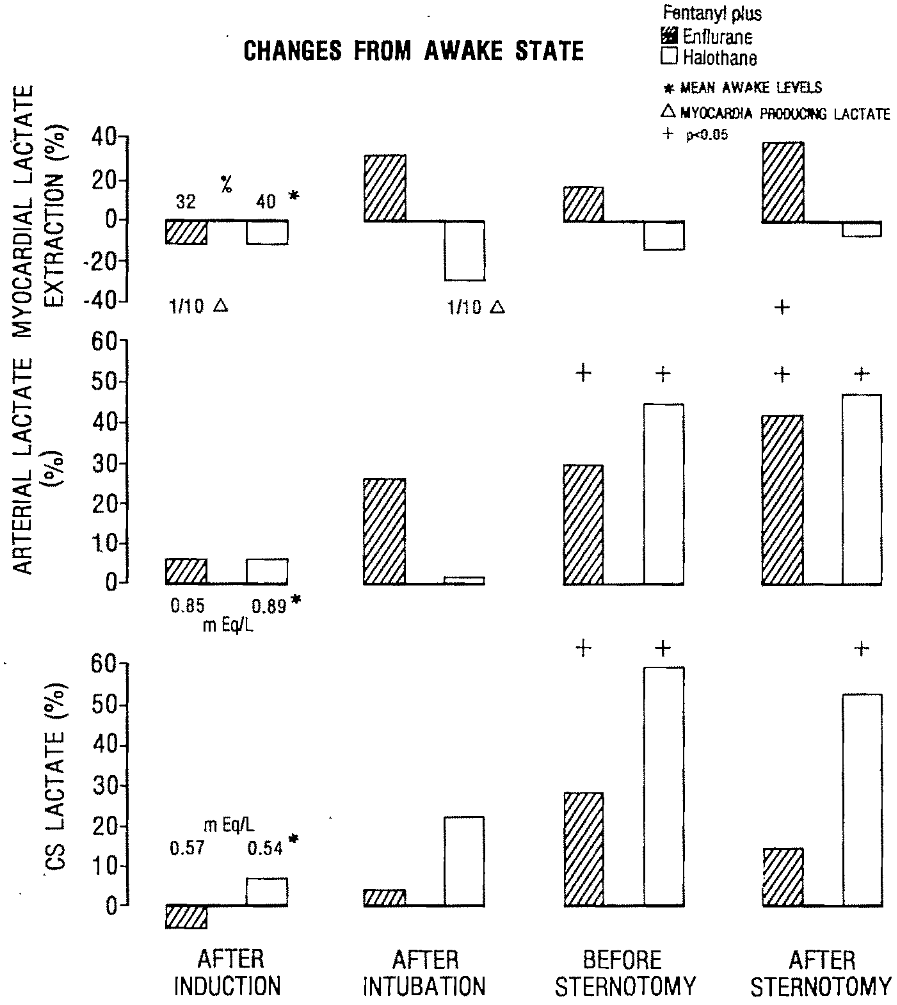

Figure 8. Percent changes from awake state in coronary sinus (CS) and peripheral arterial lactate levels and in myocardial lactate extraction. Arterial and CS lactate increased by the time of sternotomy. Myocardial lactate extraction remained unchanged, with only one heart producing lactate after induction and one after intubation.

given rapidly can cause myocardial depression in the presence of unstable pumping function.

Principles of Anesthesia Arising from this Evidence

Our studies combined with those of other investigators support the previously stated thesis and the soundness of commonly practiced low pressure–low demand anesthesia (17). With regions of compromised myocardial oxygenation, avoidance of anaerobic metabolism (ischemia) during anesthesia requires continued suppression of factors increasing oxygen need. Cardiac work and MVO_2 should be kept at or below that of the sedated awake state by starting with and keeping heart rate slow (60–70 beats/min), and by starting with and keeping arterial pressure during operation at or below the awake baseline level. Responses of the heart and circulation to anesthetic and surgical stimulation should be controlled while maintaining adequate coronary perfusing pressure (20).

No Agent Given Alone is Ideal

None of the five agents studied proved to be completely satisfactory when given alone. Enflurane and halothane with oxygen, administered in concentrations aimed at preventing hyperdynamic autonomic response, accomplished this goal with no evidence of global oxygen imbalance of the left ventricle. The problem with these inhaled agents was rapid development of hypertension on early awaking with its associated risks. High-dose fentanyl did not uniformly obtund the autonomic system but instead was associated with unpredictable episodes of hypertension on surgical stimulation, particularly in younger patients with good ventricular function (ejection fraction > 0.50). However, after a mean dose of 109 μg/kg fentanyl, little postoperative hypertension occurred. Retrospectively, the earliest (1979–80) study of Moffitt et al. (36) used an insufficient dose of morphine in incompletely β-blocked patients. The study did document that anaerobic oxygen metabolism can occur when blood pressure, heart rate, and cardiac work are not depressed at sternotomy.

Isoflurane–oxygen can also be given to maintain controlled depression of cardiac output and blood pressure. Four separate studies (15,23,48,49) raise questions related to its ability to dilate normal coronary vessels. Moffitt et al. found a significant decrease in total coronary vascular resistance on induction with isoflurane–oxygen only (23). Blood pressure decreased 33%, but coronary flow did not decrease significantly; the coronary bed dilated and maintained flow in spite of the lowered pressure. Also suggesting dilation of large portions of the coronary bed were the large increases in oxygen content of the coronary venous blood on induction that persisted through sternotomy, a phenomenon seen only with this agent. However, on induction, myocardial ischemia occurred in 30% of hearts (lactate production); mean extraction in the group decreased from 15 to 6%. Reiz et al. (48,49) and Larsen et al. (15) found myocardial ischemia in 48, 46, and 30% of their patient groups. These observations support the theory that diversion of coronary flow away from ischemic beds may occur with isoflurane in a dose-related fashion, to enhance flow through normal vessels that can dilate, with overall occurrence of regional myocardial ischemia. Based on this evidence, we presently cannot recommend the use of isoflurane in patients with coronary disease, particularly in combination with nitrous oxide. Effects of moderate doses of fentanyl with isoflurane and oxygen, given in the same manner as halothane (25) and enflurane (18), have yet to be elucidated.

When nitrous oxide was added to three commonly used agents, hemodynamic depression with a transition toward ischemia occurred, convincing us that there are real risks associated with its use (33,39). These patients were not being surgically stimulated and were adequately β-blocked at the time of study. In addition, insidious ischemia occurred unaccompanied by ECG changes. Thus we believe that CABG patients should not be exposed to this risk when it can be avoided by giving only oxygen with a potent anesthetic drug.

Maintaining a Hypodynamic Circulation until Operation

Another principle of preserving myocardial oxygenation in coronary patients is to attenuate the hemodynamic response to endogenous catecholamines by continuing β-adrenergic blockade until operation. This was shown in the study of Moffitt et al. in which 7–8 mg of propranolol were given intravenously 45 min before induction to eight patients who were not on previous β-blocker therapy (22). No adverse hemodynamic effects were seen when compared with another group of patients not similarly treated (36). In the pretreated patients (22), during anesthesia with 1 mg/kg of morphine, sternotomy produced increased SVR but no heart rate change or lactate production. The patients not pretreated who were receiving the same anesthetic had increased MAP and heart rate after sternotomy, with two of six hearts producing lactate (36).

The regular absence of hypertension and low MVo_2 on arrival in the operating room in patients studied by Moffitt et al. is good evidence of the benefits of heavy premedication. In contrast, unpremedicated patients have higher heart rate and blood pressure with increase in basal MVo_2 on arrival in the operating room (48). The effects of continuing full calcium entry blockade until the day of operation have not been studied by us, but the consistent presence of a hypodynamic circulation before and during prebypass anesthesia in our study patients confirms the correctness of that practice.

Monitoring Myocardial Oxygenation

The ideal method of simple monitoring for sensitive, early identification of myocardial ischemia is not available. There was hope from reports on awake patients (2,41) and from one study during anesthesia (67) that the product of heart rate and systolic blood pressure (rate–pressure product) would be a simple, useful indicator. But no correlation was subsequently found between RPP and MVo_2, either before or during anesthesia in CABG patients (37). Moffitt et al. also have not consistently seen ST segment or T wave changes when lactate production signalled ischemia. Elevation of heart rate and blood pressure taken together as a product does not precisely parallel MVo_2 during anesthesia, probably because increases in heart rate and systolic pressure have separate effects on MVo_2 (3). However, we believe that these two simple measurements watched separately may be the best available indirect indicators of oxygen balance. Multiple studies reviewed here show that when the heart rate is kept slow and the systolic blood pressure at or slightly below normal, myocardial oxygenation is preserved. Nevertheless, the ECG (V_5) should be monitored continuously along with PCW pressure and cardiac output, if possible, although the latter relates to cardiac function and not directly to oxygen balance.

The Best Technique: Opiate–Inhaled Agent Combination

Contrary to the diverse effects of individual agents on the circulation and myocardial oxygen supply, the effects of combining an opiate (fentanyl) with a potent inhaled agent (halothane or enflurane) in patients with good ventricular function closely approach the intended and ideal performance (18,25). Smooth depression of blood pressure was maintained in the presence of adequate β-adrenergic blockade. Cardiac index remained 20–30% below that of the awake state, with little change in systemic resistance. There were no major hemodynamic differences between the two inhaled agents enflurane and halothane (Figs. 5 and 6).

After the initial moderate dose of fentanyl, deepening the anesthetic state by reducing systolic arterial pressure by 25% for 10 min with the inhaled agent resulted in no heart rate or blood pressure response to intubation. Decreases in blood pressure on induction were beneficial because cardiac work and MV_{O_2} showed large decreases; in general no ischemia occurred. Autonomic responses to sternotomy were controlled because the anesthetic state was deepened prior to stimulation. Stroke work remained 25–40% below awake values after sternotomy, with cardiac index and blood pressure remaining decreased. Heart rate remained slow from prior β-adrenergic blockade and from fentanyl. With decreased cardiac work, more oxygen remained in coronary venous blood even though coronary flow was below normal. Coronary dilation from tissue oxygen need with higher resulting coronary flow was not present. Calculated myocardial oxygen consumption was as much as 50% below awake level. Tissue ischemia before cardiopulmonary bypass was absent because normal myocardial lactate extraction continued in all but two isolated instances. Effects of fentanyl lasted into the postoperative hours with few patients needing antihypertensive treatment.

The combined opiate–inhaled agent technique retains a hypodynamic circulation with preservation of myocardial oxygenation. After the basal opiate effects, the aim is to give the inhaled agent in order to anticipate stimulation and prevent autonomic response. The ideal, smooth hemodynamic depression is aimed for and attained. Another virtue of the combination is that if hemodynamics become depressed due to anesthetic or surgical reasons, cessation of the inhaled agent lightens the anesthetic level, improving cardiac output and systemic vascular reactivity. The technique allows a finely tuned control of the circulation.

If autonomic stimulation does break through unexpectedly, blood pressure can be reduced to an acceptable level by intravenous nitroglycerin (53). When used after sternotomy, it reduces arterial pressure, systemic resistance, and hence MV_{O_2} much more effectively than in the same patients when awake (38). Conversely, nitroprusside given for hypertension in the first postoperative hour reduces blood pressure satisfactorily by vasodilation, but does not decrease myocardial oxygen consumption (4). In patients with severe cardiac disability who develop inadequate pumping performance, dobutamine (51) by intravenous infusion or calcium chloride (21) can be given without elevating myocardial oxygen consumption more than oxygen supply.

Practices Supported by this Evidence

All investigations on myocardial oxygen balance in patients with coronary artery disease under anesthesia, with the exception of one by Reiz et al. (47), have been conducted only in patients with good ventricular function. Thus clinical practices suggested by this review apply only to this select patient subset. There are no data on patients with myocardial failure. In addition, the majority of patients studied by different investigators appear to be relatively young subjects. Accordingly, clinical practices based on this review may not apply directly to elderly patients.

The cardinal aim in anesthetizing patients with coronary lesions but with adequate pumping function is to start with and maintain a slightly depressed circulation.

An effective regimen of β-adrenergic and calcium entry blockage that keeps the circulation hypodynamic should be continued until the day of operation. If effective β-blockade is not present before induction, intravenous propranolol can be given to slow the heart rate.

Heavy premedication is needed to avoid hypertension from apprehension. Additional intravenous sedation is indicated before inserting monitoring catheters if the patient is not drowsy and relaxed. Unpremedicated patients show increased heart rate, MAP, and MV_{O_2} when compared with well-sedated patients (48).

Induction with a moderate dose of intravenous fentanyl is fast and smooth, and should be followed by a potent inhaled agent (halothane or enflurane) before intubation to prevent autonomic responses (18,25).

Arterial pressure can be maintained at or slightly below normal by the potent inhaled agent in order to anticipate and prevent hemodynamic response to surgical stimulation.

Nitrous oxide is not necessary for anesthetic purposes and involves an insidious risk of myocardial ischemia not always identified by the ECG (33,39).

Isoflurane given alone should be avoided in coronary patients because of its capacity to dilate normal segments of the coronary vascular bed in patients with coronary artery disease with the consequent occurrence of regional myocardial ischemia (15,23,48,49).

Judicious administration of intravenous nitroglycerin can help to keep blood pressure at desired depressed level while reducing cardiac work, MVO_2 and ST segment changes (38,53).

Positive inotropy for failing ventricles can be effectively produced by dobutamine infusion (51) or by intravenous calcium chloride (21) given slowly, without upsetting myocardial oxygen balance.

Regarding monitoring during anesthesia, the blood pressure (kept at or below baseline) and the heart rate (kept < 70 beats/min) are simple and reliable means of preserving myocardial oxygen balance distal to coronary lesions.

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Clinical Reports

Midtracheal Obstruction after Harrington Rod Placement in a Patient with Marfan's Syndrome

Robert B. Mesrobian, MD, and Jerry L. Epps, MD

Marfan's syndrome and its constellation of findings present several problems for anesthesiologists (1–3). We encountered a youth with this syndrome who developed a life-threatening tracheal obstruction—a previously unreported complication of Harrington rod placement (4,5).

Case Report

A 16-yr-old male underwent posterior spinal fusion and Harrington rod placement for correction of severe scoliosis. He exhibited Marfan's syndrome manifested by arachnodactyly, ectopia lentis, mitral valve prolapse, ascending aortic arch dilation, pectus excavatum, and scoliosis. Preoperative pulmonary function tests revealed a forced vital capacity (FVC) of 2.5 L (56% of predicted), a forced expired volume in 1 sec (FEV1) of 1.71 L (40% of predicted), and an FEV1/FVC ratio of 66% consistent with a mild obstructive ventilatory defect. His arterial blood gas levels while breathing room air included a pH of 7.41, Pa_{O_2} of 108 mm Hg, and Pa_{CO_2} of 35 mm Hg.

After premedication with diazepam, 10 mg orally, radial artery cannulation and insertion of a central venous catheter were performed. General anesthesia was induced with 250 mg thiopental, followed by 80 mg succinylcholine intravenously. Tracheal intubation was accomplished without difficulty. Anesthesia was maintained with fentanyl–pancuronium–nitrous oxide–oxygen.

The patient was in the prone position with his chest supported by two lateral rolls. Controlled respiration required peak airway pressures exceeding 50 cm H_2O, and even they produced minimal chest excursion. There were no apparent physical or mechanical problems. Readjusting the lateral chest rolls to support the lower thorax resulted in return of peak airway pressure to 20 cm H_2O. Because a reinforced endotracheal tube was not used, it was assumed prior positioning had resulted in kinking of the endotracheal tube. The remainder of the operation proceeded uneventfully. At the end of the operation, the patient was turned to the supine position. While breathing spontaneously, the respirations became labored with increased inspiratory effort. Attempts at assisted ventilation met with marked resistance to positive pressure. Suspecting an obstructed endotracheal tube, we extubated the patient (the lumen of the tube was patent) and attempted mask ventilation with minimal success. Direct laryngoscopy was then performed. The glottis and vocal cords appeared normal. The trachea was rapidly reintubated and ventilation accomplished with ease. Peak airway pressure again averaged 20 cm H_2O.

In the recovery room, during intermittent mandatory ventilation, the patient developed bilateral rales, an S3 gallop, and hypoxemia while breathing 40% oxygen in air (Pa_{O_2} decreased to 63 mm Hg from 200 mm Hg). A chest radiograph at this time was consistent with the diagnosis of pulmonary edema. Treatment with 5 mg furosemide intravenously initiated a diuresis of greater than 3 L over the next 4 hr. Eight hours after surgery, the patient, still intubated, was breathing comfortably through a T-piece with a respiratory rate of 12 breaths/min. Bedside spirometry revealed an FVC of 1.2 L with arterial blood gas values

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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Address correspondence to Dr. Mesrobian, Anesthesia and Operative Service, Walter Reed Army Medical Center, Washington, D.C. 20307-5001.

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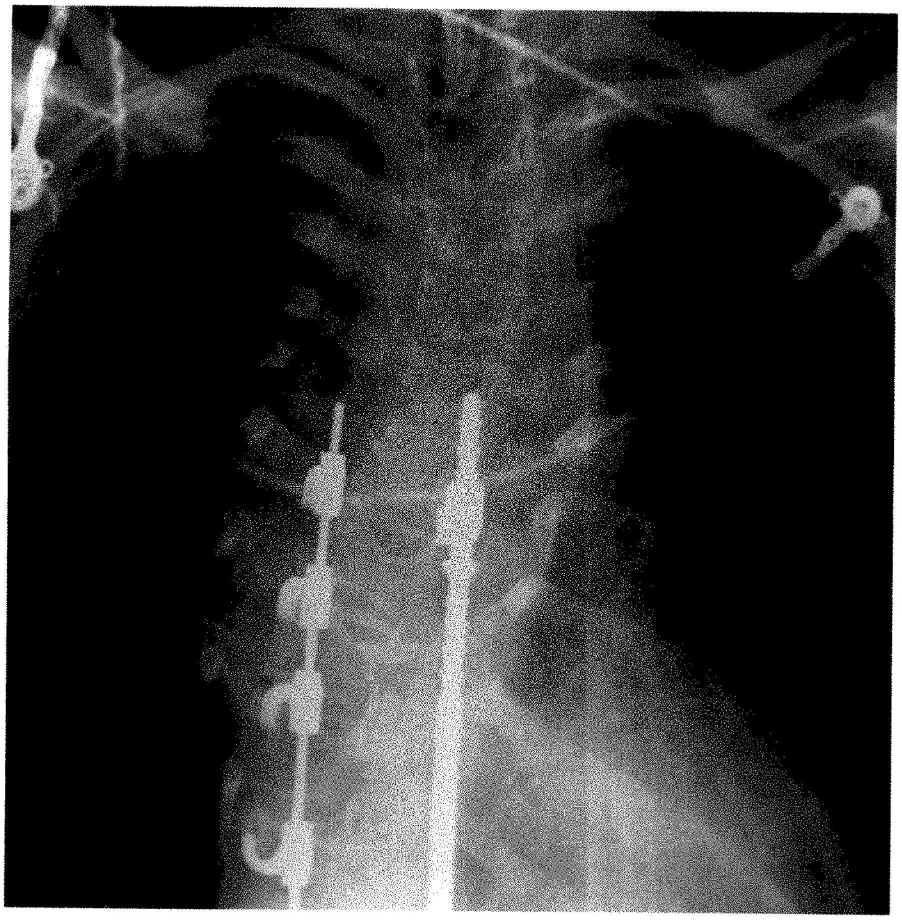

Figure 1. Postoperative AP chest radiograph. Note that the midtracheal air column is absent.

(F_{IO_2} 0.4) of pH 7.5, Pa_{O_2} 214 mm Hg, and Pa_{CO_2} 31 mm Hg. The patient was extubated and did well for 2 hr. He then developed tachycardia, stridor, and arterial hypoxemia (Pa_{O_2} 48 mm Hg). Thiopental and succinylcholine were given and tracheal intubation performed under direct laryngoscopy. No glottic abnormality or edema was noted. Immediately after intubation, attempts at ventilation met marked resistance consistent with an obstructed airway. Mask ventilation after subsequent suctioning and extubation were also unsuccessful. Repeat laryngoscopy and intubation were again performed. Positive pressure ventilation was now successful without evidence of obstruction.

Because of the documented episodes of apparent airway obstruction below the endotracheal tube or at its tip an extensive review of this patient's respiratory history was made. He informed us of a preference to sleep in the supine rather than the prone position preoperatively. A preoperative lateral chest radiograph revealed lordosis of the thoracic spinal column with close approximation of the sternum and thoracic vertebrae at the level of the thoracic outlet. A postoperative anterior–posterior chest radiograph showed complete loss of the tracheal air column at the same level (Fig. 1). Two-dimensional cinematography revealed compression of the midtracheal air column between the sternum and the first and second thoracic vertebrae. This compression was most marked with the patient in the prone position. Bronchoscopy, performed on the fifth postoperative day, revealed rotation of the midtrachea with the noncartilaginous portion located at the 9 o'clock position (6 o'clock normal), as well as marked anterioposterior narrowing. Prominent aortic pulsations were seen at the area of tracheal narrowing. After bronchoscopy on the fifth postoperative day, the patient was extubated and went on to an uneventful postoperative recovery. Postoperative pulmonary function testing after removal of the patient's body cast showed a return to baseline spirometric values. In addition, flow volume loops done in standing, prone, supine, and lateral decubitus positions showed decreased expiratory flow in the supine and prone positions.

Discussion

Marfan's syndrome, an autosomal dominant trait, is characterized by generalized connective tissue defects. Although the specific biochemical abnormality has yet to be identified, it results in a lack of tensile strength and increased elasticity of the connective tissue matrix. The lack of connective tissue strength leads to the variety of abnormal physical findings mentioned above. Also, degeneration of the medial elastic fibers of the large blood vessels, which leads to the formation of aneurysms and disproportionate bone growth, is often seen. The latter leads to the well-known increased arm span and arachnodactyly as well as to scoliosis and pectus excavatum.

In the case described above, it appears that a connective tissue defect contributed to life-threatening airway obstruction. We propose that the structurally weakened trachea with anterior–posterior narrowing from aortic root dilation caused intermittent obstruction depending on whether the endotracheal tube tip was above or below the compression. The patient's history of a preference for sleeping in the prone position indicated that the problem was present preoperatively. Postoperative flow volume loops showed decreased expiratory flow in the prone and supine positions that were significantly greater than preoperative values. Review of radiographs both before and after the operation show loss of the midtracheal air column after the operation. The possibility that the placement of Harrington rods increased intrathoracic obstruction by closer approximation of the sternum and vertebral column in a patient with increased costochrondral flexibility must be considered.

Tracheal intubation failed to relieve the obstruction on two occasions. Most likely this occurred because the tip of the tube, due to its beveled configuration, was at the area of narrowing and resulted in obstruction of the tube. Indeed, when the tube was advanced farther into the trachea on a subsequent intubation, no obstruction was present. Alternatively, the presence of a rigid endotracheal tube in a trachea with an already narrowed and weakened segment may have further narrowed that segment by torsion. Should this complication be encountered by others, we recommend that the endotracheal tube be advanced beyond the point of narrowing. Because this may result in mainstem intubation, the use of a double-lumen endotracheal tube may be required.

Despite the observation that the narrowing lay at the level of the midtrachea (between the upper sternum and vertebral bodies), the patient appeared to have symptoms of both intra- and extrathoracic obstruction. Although postoperative flow volume loops showed a prolonged expiratory phase (indicating intrathoracic obstruction), the patient also exhibited clinical signs of extrathoracic obstruction during these episodes.

During the operation, fluid management was based on serial measurements of hematocrits, central venous pressure, urine output, and calculated fluid balance. The dependent position of the extremities may have led to a sequestered third-space loss that manifested as pulmonary edema in the recovery room. We believe this contributed to further narrowing of the tracheal lumen due to edema. Indeed obstruction was significantly less on the fifth postoperative day, after maximal diuresis had occurred and the patient had nearly returned to preoperative weight.

In summary, we have presented a case of midthoracic tracheal obstruction in a patient with Marfan's syndrome that was exacerbated during posterior spinal fusion and insertion of a Harrington rod. The etiology of this obstruction most likely represents a combination of some of the components of Marfan's syndrome, including structural weakness of cartilaginous structures such as the sternochondral junction and the trachea, dilation of the aortic root, and abnormal vertebral curvature. We believe that anesthetic management of patients with Marfan's syndrome must now include consideration of the possibility of midtracheal obstruction. Closer attention not only to eliciting a history of dyspnea in various positions, but review of the tracheal air column on preoperative radiographs and pulmonary functions tests with flow volume loops in standing, prone, and supine positions should be routine in patients with Marfan's syndrome undergoing posterior spinal fusion for correction of scoliosis.

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Amiodarone-Induced Sinus Arrest Successfully Treated with Ephedrine and Isoproterenol

Ashok A. Navalgund, MD, James K. Alifimoff, MD, Andres J. Jakymec, MD, and Achiel L. Bleyaert, MD

Amiodarone is an antiarrhythmic agent that is effective against a wide spectrum of tachyarrhythmias. Properties of this drug that may create problems for the anesthesiologist include myocardial depression (1,2), peripheral vasodilation and hypotension (3–5), prolonged duration of action (3), and atropine-resistant bradycardia (6). Sinus arrest secondary to amiodarone administration has been reported in four patients, all of whom required ventricular pacing for treatment (7–9). None of these four patients were anesthetized, but we recently encountered sinus arrest during anesthesia in a patient who was taking amiodarone for refractory atrial fillibration. The arrest was treated successfully with ephedrine and isoproterenol.

Case Report

A 71 yr-old, 47-kg woman with a long history of peripheral vascular disease underwent elective surgery for right femoral popliteal bypass grafting. Her medical history was remarkable for a nonparkinsonian extrapyramidal tract disorder treated with carbidopa, levodopa, and amantadine hydrochloride; diabetes mellitus controlled with chlorpropamide; and atherosclerotic coronary artery disease with paroxysmal atrial fibrillation treated with digoxin (0.125 mg/day) and amiodarone (200 mg/day).

Preoperatively, blood pressure (BP) ranged from 130/60 to 140/80 mm Hg and heart rate (HR) from 52 to 56 beats/min. Physical examination was remarkable for the absence of pulsations in the right posterior tibial and dorsalis pedis arteries and atrophic skin changes of the right lower extremity. Electrocardiogram showed a sinus bradycardia with a first-degree atrioventricular block at a rate of 54 beats/min. Chest roentgenogram and findings from routine laboratory tests were normal. Serum digoxin level was 0.7 ng/ml.

The last dose of amiodarone had been given on the day before surgery. The patient was premedicated intramuscularly with hydroxyzine (75 mg), 1 hr before the anticipated operation. On arrival in the operating room, the patient was very apprehensive, with BP of 200/90 mm Hg and HR of 56 beats/min. Diazepam (3.75 mg) and fentanyl citrate (100 μg) were administered intravenously in incremental doses, and BP decreased to 130/90 mm Hg while HR remained unchanged. Anesthesia was induced intravenously with thiopental (175 mg in incremental doses), after intravenous precurarization with *d*-tubocurarine (3 mg). Tracheal intubation was facilitated with succinylcholine, 100 mg intravenously, and anesthesia maintained with 0.5% enflurane and 60% nitrous oxide in oxygen. The patient's HR ranged from 56 to 60 beats/min and BP from 120/60 to 130/70 mm Hg.

Two and one half hr after induction, sinus arrest of several seconds duration occurred with the spontaneous resumption of a junctional rhythm at a rate of 26 beats/min. The patient appeared poorly perfused, and BP decreased to 70/40 mm Hg. Initial treatment was with atropine sulfate (2 mg intravenously in incremental doses), without effect. Incremental doses of ephedrine to 25 mg intravenously increased HR to 54 beats/min and BP to 140/85 mm Hg. Arterial blood gas analysis at this time ($F_{I_{O_2}}$ 1.0) showed pH, 7.39; Pa_{O_2}, 153 mm Hg; Pa_{CO_2}, 41 mm Hg; HCO_3^-, 24 mEq/L; and base excess (BE), −1. Serum Na^+ and K^+ were 135 mEq/L and 3.4 mEq/L, respectively. Twenty-five min later, HR again decreased to 40 beats/min with a BP of 90/60 mm Hg. Isoproterenol (10 μg intravenously) was administered with a subsequent increase in HR to 90 beats/min and in BP to 150/80 mm Hg. Within 10 min, HR again slowed to

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Address correspondence to Dr. Navalgund, Department of Anesthesiology and Critical Care Medicine, Presbyterian-University Hospital, DeSoto and O'Hara Streets, Pittsburgh, PA 15213.

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50 beats/min. Isoproterenol (2 μg intravenously) increased the rate to 65–70 beats/minute.

One hour later, the patient was admitted to the recovery room. Her vital signs on admission were BP, 170/85 mm Hg; HR, 50 beats/min; respiratory rate, 16 breaths/min; and axillary temperature, 35°C. A 12-lead ECG showing a sinus bradycardia at a rate of 52 beats/min was otherwise unchanged from the preoperative ECG. Serum electrolyte levels were normal, with the exception of a potassium level of 3.3 mEq/L for which potassium chloride was given intravenously. Blood glucose level was 185 mg/dl and hematocrit 34%. Arterial blood gas analysis while the patient spontaneously breathed 40% oxygen via a T-piece attached to the endotracheal tube showed pH, 7.45; Pa_{O_2}, 128 mm Hg; Pa_{CO_2}, 28 mm Hg; HCO_3^-, 19 mEq/L; and BE, −3.

Approximately 50 min after admission to the recovery room, HR decreased to 40 beats/min and BP to 85/60 mm Hg. The rhythm at this time was sinus bradycardia. Isoproterenol (10 μg) was given intravenously, and an infusion of isoproterenol at a rate of 4–24 μg/hr was started to maintain HR at 60–68 beats/min and BP at 120/60–140/70 mm Hg. The patient was successfully weaned from isoproterenol infusion 16 hr postoperatively. Her ECG was monitored for 24 hr, and she was then discharged after an otherwise uneventful postoperative course on the seventh postoperative day.

Discussion

Amiodarone, originally introduced in Europe as a coronary vasodilator, is an effective agent for the suppression of both supraventricular and ventricular tachyarrhythmias (10,11). Although it has a multiplicity of electrophysiologic actions, such as prolongation of sinus node recovery time (12) as well as intraatrial conduction time (13) and atrioventricular node refractory period (13), amiodarone's major effects are on the atrium and on duration of ventricular action potential (14). The latter effects can result in a clinically significant sinus bradycardia (15); indeed atropine-resistant sinus bradycardia (6), sinoatrial block (16), and sinus arrest (7–9) have been reported.

A probable mechanism of amiodarone-induced sinus arrest is inhibition of phase 4 depolarization of the sinus node (17). Thus the potential exists for interaction between amiodarone and anesthetics that inhibit sinus node automaticity. Enflurane probably did not contribute to the sinus arrest in our patient because no deleterious effects of this agent on sinoatrial node activity have been documented. Krishna and Paradise (18) have, in fact, shown that enflurane elicits a dose-dependent positive chronotropic effect on isolated rat atria. Halothane, however, reduces phase 4 depolarization in the sinoatrial node (9–12, 19) and might potentiate the effects of amiodarone on the sinoatrial node. To our knowledge, this potential adverse interaction has not been investigated.

Another class of drugs that may possibly interact adversely with amiodarone are the antiarrhythmic agents themselves. Jones (20) speculated that amiodarone-induced sinus arrest might be secondary to amiodarone–digoxin interaction. Although amiodarone enhances digoxin action by displacing digoxin from its protein binding sites (21), sinus arrest has been reported in a patient who was taking only amiodarone (9). Although amiodarone may increase serum digoxin concentration by as much as 70%, digoxin concentration in our patient was 0.7 ng/ml (lower limit of therapeutic level). Keiden et al. (22) observed a patient in whom sinoatrial arrest developed after injection of 120 mg of lidocaine for local anesthesia. They hypothesized that the interaction between lidocaine and amiodarone, both of which depress sinoatrial node activity, was responsible for the arrest. Thus other antiarrhythmic agents, such as quinidine, that depress diastolic depolarization of the sinoatrial node may interact with amiodarone, suppress impulse formation, and produce sinoatrial arrest.

In all four of the cases of sinus arrest reported in the literature (7–9), ventricular pacing was needed to correct the sinus arrest. Responses to isoproterenol or other chronotropic agents were not reported. The sinus arrest in our patient responded to ephedrine, and the bradycardia that occurred later responded to isoproterenol. One should, however, be prepared to initiate ventricular pacing during anesthesia if sinus arrest occurs in patients taking amiodarone.

On the basis of the present case, we recommend that a pacemaker be inserted for elective surgery under general anesthesia in a patient taking amiodarone. The half-life of amiodarone is 30 days, and its pharmacologic effects may last as long as 45 days (2). Thus an alternative to using a pacemaker would be to postpone surgery for 45 days and discontinue amiodarone during that time. However, because the drug is generally given when conventional antiarrhythmic agents have proved ineffective, discontinuation may not be possible.

In summary, we present this case to alert anesthesiologists that sinus arrest can occur during general anesthesia in patients treated with amiodarone, possibly as a result of drug interaction, and to describe its successful treatment with ephedrine and isoproterenol.

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Ventricular Arrhythmias after Terbutaline Administration to Patients Anesthetized with Halothane

Somasundaram Thiagarajah, MD, FFARCS, Michael Grynsztejn, MD, Erwin Lear, MD, and Isaac Azar, MD

Halothane is considered by many to be the anesthetic of choice for asthmatic patients because of its bronchodilator action (1,2). If wheezing occurs in patients during halothane anesthesia, the administration of a bronchodilator drug may be necessary (3). Halothane, when combined with aminophylline, enhances the sensitivity of the myocardium to catecholamines and may induce ventricular arrhythmias (4). Terbutaline, a bronchodilator, is considered to be predominantly a β_2-adrenergic agonist and therefore is presumed to be less arrhythmogenic than other bronchodilators such as epinephrine or aminophylline. Terbutaline would seem a rational choice as a drug to treat bronchospasm occurring in patients during halothane anesthesia (5). Adverse interactions producing arrhythmias have not been described when terbutaline was administered for the treatment of bronchospasm in patients anesthetized with halothane. This report describes two patients who developed ventricular arrhythmias when terbutaline was administered to relieve bronchospasm during halothane anesthesia.

Case Reports

Case 1

A 45-yr-old, hypertensive, 100-kg female was scheduled for cholecystectomy and cholangiogram. She had a long history of wheezing attributed to her 50 pack-years (two packs per day for 25 yr) of cigarette smoking. Wheezing was easily controlled with oral medication, and neither hospitalization nor emergency room treatment had been required. The preoperative physical examination and laboratory data were all within normal limits. The arterial blood gases while the patient was breathing room air were pH 7.46, Pa_{CO_2} 36 torr, and Pa_{O_2} 74 torr.

The patient was premedicated with meperidine, 50 mg and droperidol, 5 mg intramuscularly, 1 hr before the operation. She received 300 mg of oral cimetidine the night before and again prior to surgery. Anesthesia was induced with incremental doses of fentanyl (250 μg) and thiopental (500 mg). Tracheal intubation was accomplished after administration of succinylcholine (100 mg). Anesthesia was maintained with an inspired concentration of 2–3% halothane, in 50% O_2 with N_2O. Muscle relaxation was achieved with pancuronium. Within 10 min of the onset of surgery, wheezing was detected by auscultation, and the patient was given 0.35 mg of terbutaline subcutaneously. Within the next 20 min, the wheezing completely disappeared, but her heart rate increased from 68 to 100 beats/min and her ECG revealed unifocal premature ventricular contractions followed by bigeminy. Her temperature was 37.2°C; an arterial blood specimen showed a pH of 7.43, a Pa_{O_2} of 116 torr, a Pa_{CO_2} of 35 torr, and potassium concentration 4.1 mEq/L. There had been no surgical stimulation during this period. The ventricular arrhythmia responded to a 100 mg bolus of intravenous lidocaine, and the subsequent anesthetic course was uneventful. She developed wheezing again in the recovery room and responded to aminophylline.

Case 2

A 52-yr-old male was scheduled for colon resection. He had been wheezing intermittently since childhood, but wheezing was easily controlled with nebulized isoetharine. He had been free of symptoms for more than 2 yr. Premedication consisted of meperidine, 50 mg, and hydroxyzine, 25 mg. Anesthesia was induced with fentanyl, 200 μg, droperidol, 5 mg, and divided doses of thiopental totalling 450 mg. Tracheal

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Address correspondence to Dr. Thiagarajah, Department of Anesthesiology, Beth Israel Medical Center, First Avenue at 16th Street, New York, NY, 10003.

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intubation was achieved after administration of succinylcholine, 100 mg. Anesthesia was maintained with halothane in N_2O with 50% oxygen. Immediately after intubation, the patient developed a bout of wheezing that responded to terbutaline, 0.25 mg, administered subcutaneously. The patient developed multiple unifocal premature ventricular contractions and bigeminy within the next 25 min. The arrhythmias responded to intravenous lidocaine therapy. Halothane was discontinued and enflurane started. An arterial blood sample during this period revealed a pH of 7.37, a PaO_2 of 186 torr, a $PaCO_2$ of 31 torr, and a potassium concentration of 3.9 mEq/L. The subsequent anesthetic course was uneventful.

Discussion

Ventricular arrhythmias can occur in the perioperative period because of inherent cardiac irritability, hypoxia, hypercarbia, hypothermia, potassium imbalance, or adverse drug interactions, such as halothane–epinephrine (6), halothane–aminophylline (4), halothane–tricyclic-antidepressants–pancuronium (7), and hypercarbia–neostigmine (8) or naloxone (9).

When patients develop wheezing during halothane anesthesia, the first treatment is to deepen anesthesia, provided blood pressure is stable, and to eliminate common causes (e.g., secretions, obstruction, carinal stimulation, soda-lime dust, foreign body, pneumothorax). If bronchospasm persists, the use of nebulized isoetharine or metaproterenol should be considered. The judicious use of subcutaneous terbutaline or intravenous aminophylline has been suggested if wheezing continues to persist (10). Halothane may have to be discontinued to prevent arrhythmias, and enflurane or isoflurane may be substituted when bronchodilators with chronotrophic effect are administered parenterally.

Originally, terbutaline was thought to be a specific β_2-adrenergic agonist with minimal effect on the cardiovascular system. It has been observed, however, that terbutaline causes vasodilation with compensatory tachycardia (10). The onset of the action of terbutaline is relatively slow (30–60 min) and therefore its use for the rapid relief of bronchospasm has been questioned (10). Additionally, terbutaline combined with halothane may produce arrhythmias even in the normocarbic normoxic patient, as demonstrated in the two cases reported herein. We therefore caution against the use of terbutaline in patients who are anesthetized with halothane.

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Letters to the Editor

Double Internal Jugular Vein Cannulation in Pediatric and Adult Cardiac Surgery Patients: An Easy and Convenient Technique

To the Editor:

Many patients undergoing cardiac surgery require the simultaneous administration of several medications by continuous intravenous infusion. Because it is preferable that many of these be administered centrally, particularly when the arms are covered by surgical drapes, the internal jugular vein (IJV) has been popularized for ease of central venous access. In adult patients, however, if a pulmonary artery catheter (PAC) is placed in a single 8.5F sheath inserted percutaneously into the IJV, a limited number of ports is available for administration of blood and drugs: 1) the side port of the 8.5F sheath, 2) the central venous (CV) port of the PAC, and 3) the extra venous port of the PAC, if such a catheter is used. Clearly, if a number of infusions must be administered simultaneously, this system is inadequate. In pediatric patients, a single venous line cannot be used simultaneously for administration of intravenous drips and for the continued monitoring of central venous pressure (CVP).

In order to overcome the disadvantages of single venous cannulation, we have modified the technique described by English et al. (1) to insert two central venous catheters into the same IJV.

For adult patients, after a J-wire (Arrow Percutaneous Sheath Introducer Kit, Arrow International, Inc., Reading, PA) is inserted into the IJV through an 18-gauge over-the-needle catheter, the catheter is withdrawn. A second 18-gauge over-the-needle catheter is inserted into the IJV 1 cm above or below the point where the indwelling J-wire penetrates the skin. The position of the J-wire provides a guide to the location of the IJV, and the operator can simply direct the second 18-gauge catheter to a subcutaneous point where it appears it will intersect the J-wire. Once venous position of the second 18-gauge catheter is confirmed, a second J-wire is inserted and the catheter is removed. A small incision is then made where each J-wire enters the skin, and a purse-string suture is placed around each wire. An 8.5F sheath-dilator unit with side port/hemostasis valve catheter to sheath adapter is passed over each J-wire, the dilators are removed, and the positions of the 8.5F sheaths are secured with the indwelling sutures. It is important that the sutures be placed prior to insertion of the two 8.5F sheaths, because attempting to sew them in afterwards may result in inadvertent perforation of the thin-walled sheaths.

After both sheaths are in position, a PAC is placed in one and an Arrow–Howes multi-lumen CV catheter (Arrow International, Inc.) in the other. This yields a total of 6 or 7 ports for administration of drugs and fluids simultaneously: (**A** and **B**), the side arm on each of the 2 sheaths; (**C**), 3 ports on the multi-lumen CV catheter; and (**D**), 1 or 2 ports on the PAC, depending on the type inserted (Fig. 1).

For pediatric patients, after the right IJV is located with a 22-gauge over-the-needle catheter, a J-wire supplied in the Cook tray (CDLMY-501J-PED-BH, Cook Inc., Bloomington, IN; Cook Catheter, 5.0 French, 5 cm in length) is inserted through the catheter and the catheter is withdrawn. A second 22-gauge catheter is inserted just above or below the first wire as described in adult patients. A second J-wire is inserted and the catheter is removed. A double-lumen catheter is then passed over each J-wire and the J-wires are removed. The Cook catheters are positioned in place with appropriate sutures to the skin. This yields a total of four ports—three for administration of drugs and fluids and one for continuous monitoring of CVP (Fig. 2).

During the past three years, we have performed more than 2000 double IJV cannulations in adult patients and more than 100 in pediatric patients (new-borns–5 yr) without sequelae. Using a Doppler ultrasonic velocity detector operating at a frequency of 5 MHz (MedaSonics ultrasonic stethoscope, model BF4A, Mountain View, CA), we confirmed patency of the IJV preoperatively and 5 days postoperatively in 35 consecutive adult patients having double IJV cannulations.

In our hands, this technique requires only a few minutes more than single cannulation. Not only do we obtain an adequate number of ports for simultaneous administration of more than one vasoactive and/or inotropic infusion during intra- and postoperative periods, but also the patient does not usually require any other venous cannulation in the postoperative period. Because of the large diameter of

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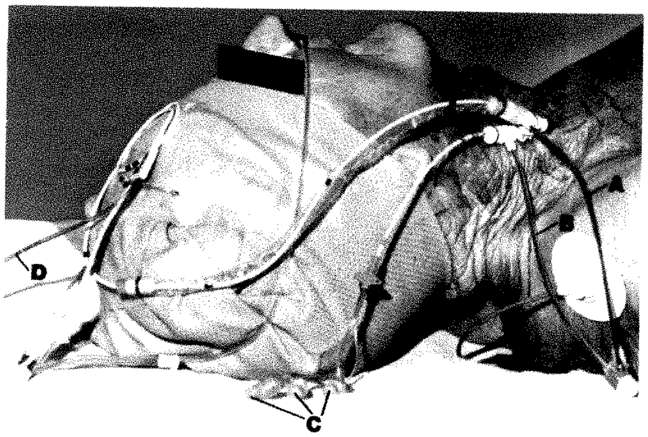

Figure 1. Patient with double internal jugular vein cannulation providing six additional CV ports: (**A** and **B**), side ports of 8.5F sheaths; (**C**), three ports of multi-lumen CV catheter; and (**D**), intravenous proximal (CV) port of PAC.

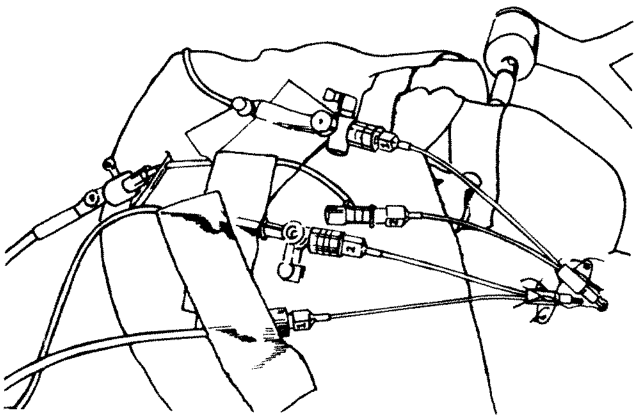

Figure 2. Pediatric patient with two double-lumen catheters in the internal jugular vein.

the IJV, intravenous administration of antibiotics does not cause the phlebitis commonly seen in peripheral veins. Additionally, the anesthesiologist may inspect the site of cannulation throughout the surgical procedure, eliminating the undetected infiltration or disconnection of lines which occurs with peripheral venous lines hidden under the surgical drapes.

Judith A. Fabian, MD
M.C.S. Jesudian, MD
Kang H. Rah, MD
Department of Anesthesiology
Medical College of Virginia
Virginia Commonwealth University
Richmond, VA 23298

Reference

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Temperature Correction of Blood Gas Tensions?

To the Editor:

Reading Dr. Sladen's article "Temperature and Ventilation after Hypothermic Cardiopulmonary Bypass" (1) renews in my mind the controversy regarding whether blood gas tensions should be "corrected" to the patient's temperature or merely interpreted at 37°C, where they are analyzed in the clinical laboratory. Dr. Sladen chose to correct blood gas tensions to the patients' actual temperatures. This choice will tend to make the blood gas tensions appear to change more dramatically as the patients rewarm in the intensive care unit after open heart surgery, but in my mind it confuses the issue.

If one cools a sample of normal blood (i.e., pH 7.40, P_{CO_2} 40 mm Hg) from 37 to 34.7°C, the reported average patient temperature upon arrival in the Stanford ICU (1), the pH will increase and the P_{CO_2} will decrease. The corrected values will be pH 7.43 and P_{CO_2} 36 mm Hg. The pH increases because water is less dissociated into OH^- and H^+ at the lower temperature. As $[H^+]$ decreases with cooling, so does $[OH^-]$. The *overall* acid–base status in this closed system is unchanged (2) despite an increasing pH and a decreasing P_{CO_2}.

The P_{CO_2} decreases with cooling of the blood because 1) CO_2 content is constant in this closed system and 2) carbon dioxide becomes more soluble as the temperature decreases. When solubility is increased, a lower gas partial pressure is in equilibrium with the unchanged gas content.

From Dr. Sladen's data, I infer that 17% of his patients entered the ICU with a temperature less then 33.8°C. If a sample of their blood read at 37°C were pH 7.40 and P_{CO_2} 40 mm Hg, their corrected values would be pH 7.447 and P_{CO_2} 34.8 mm Hg.

$$\text{Corrected pH} = \text{pH}_{(37°)} + 0.0147\,(37 - \text{temp});$$

$$\text{Corrected } P_{CO_2} = P_{CO_2(37°)} \times 10^{0.019\,(\text{temp} - 37)}$$

Thus they would have been considered "hyperventilated" by Dr. Sladen. Should they be?

A strong argument against correction of blood gas tensions to patient temperature is made by Ream et al. (3). They cite Rahn (4), who recommends keeping human serum slightly alkaline to the neutral point regardless of body temperature. This will maintain the intracellular medium at or near the neutral point. This in turn preserves the charge state of the proteins important for cellular function. The easiest way to know what pH to aim for at various temperatures to maintain this slight alkaline offset is to aim for a normal pH at 37°C.

Ream et al. also recommend maintaining minute ventilation, despite a decrease in the patient's temperature, with an aim to keep the P_{CO_2} 40 mm Hg when the sample is read at 37°C. They cite animal studies reporting better cardiac function, appropriate cerebral blood flow, and maintenance of cerebral blood flow autoregulation in the most sensitive range when this method of interpretation is used. They also refer to their experience suggesting less ventricular irritability in patients cooling prior to cardiopulmonary bypass.

Table 1. Corrected and Noncorrected Paco$_2$ and Temperature (Case Number 42)

Hours after admission	0.5	2	4	5	6.5	11.5
Rectal temperature	31.8	33.2	33.5	34.6	36.5	37.6
VE (L/min)	7.8	7.8	7.8	10.4	10.4	10.4
Paco$_2$ (corrected)	33	35	47	44	45	33
pH (corrected)	7.46	7.43	7.30	7.36	7.36	7.48
Paco$_2$ (noncorrected)	42	42	55	49	46	32
pH (noncorrected)	7.42	7.37	7.25	7.32	7.35	7.49

VE, delivered mechanical ventilation.

The controversy continues to rage, apparently even within the walls of one university! Dr. Sladen suggests that patients' ventilatory needs may change as they rewarm, and that patient shivering probably dictates the need for increased ventilation. I don't know how much of his conclusion is based upon his interpretation of his patient data, which is at variance with the recommendation by Ream et al.

Stuart T. Anderson, MD
Steven J. Barker, PhD, MD
Department of Anesthesiology
University of California, Irvine Medical Center
Orange, CA 92668

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In Response:

The questions asked by Drs. Anderson and Barker are germane, but they do not make the problem quite disappear. Their inference is that the alkalosis on admission and the acidosis during rewarming are artifactual, and appropriate to the patient's temperature if noncorrected arterial blood gas tensions were used. Indeed, a mild degree of hyperventilation in cold patients on admission to the intensive care unit may not be harmful and may protect against subsequent hypoventilation during rewarming. However, as is illustrated in data from a typical patient (Table 1), the increase in Paco$_2$ *precedes* the maximum elevation in temperature. In patients who became hypercarbic in the postoperative period, peak Paco$_2$ occurred at a mean of 4.6 hr after admission to the ICU, whereas maximum rewarming took a mean of 8 hr. Although the use of noncorrected Paco$_2$ values mitigates the effect of alkalosis on admission (Paco$_2$ 33 mm Hg and pH 7.46 become 42 mm Hg and 7.42, respectively), it actually enhances the degree of acidosis during rewarming (Paco$_2$ 47 mm Hg and pH 7.30 become 55 mm Hg and 7.25, respectively). Respiratory acidosis remains a potential postoperative problem whether or not blood gases are corrected to patient temperature.

Robert N. Sladen, MB
Department of Anesthesia
Stanford University Medical Center
Stanford, CA 94305

Intravascular Injection of Local Anesthetic after Venipuncture of Axillary Vein during Attempted Brachial Plexus Block

To the Editor:

A healthy 56-yr-old man who presented with Dupuytren's contracture of his right ring finger agreed to an axillary brachial plexus block. While attempting arteriotomy of the axillary artery with a 23-gauge short-bevel needle venipuncture of the axillary vein was performed. Because this vein also lies in the interfascial compartment, the decision was made to deposit 45 ml of local anesthetic solution (0.50% bupivicaine with 1:400,000 fresh epinephrine) about it, 30 ml posteriorly and 15 ml anteriorly. After the uneventful posterior injection, the needle was slowly withdrawn through the venous lumen until aspiration showed its tip to be outside the anterior wall of the vein. Before receiving the second injection the patient had a grand mal seizure that was quickly stopped by the intravenous injection of 50 mg of thiopental. He was easily ventilated with 100% oxygen by mask during this episode, fully recovering without apparent sequelae.

I believe there were two reasons for this complication. First, the muscular layer of the axillary artery is thicker than that of the axillary vein. After arteriotomy, an arterial wall behaves analogously to a self-sealing tire after removal of a nail. Venipuncture, I believe, is more likely to leave a patent opening in the wall of the vessel. Second, perivascular injection of a large volume of local anesthetic may cause a pressure within the interfascial space higher than the relatively low value found within the vein. The combination of these two factors may cause local anesthetic to flow into the vein after the needle is withdrawn.

What ought to be done after venipuncture of a vein lying in the brachial plexus interfascial space? I suggest withdrawing the needle completely and waiting several minutes before further exploration to allow a clot to form at the venipuncture site. The site should not be massaged after the local anesthetic is injected to help prevent the fresh clot from losing its integrity. These procedures should reduce the chance of an intravenous injection.

Ernest R. Greene Jr, MD, PhD
Department of Anesthesiology
Veterans Administration Medical Center and
University of Alabama at Birmingham
Birmingham, AL 35294

Measures of Outcome

To the Editor:

I would like to comment on Dr. Reves' letter to the editor (Anesth Analg 1985;64:751) in which he says that it is "better" to study preservation of ventricular contractility and diastolic compliance than it is to look at outcome in terms of morbidity and mortality. It is my view that we have reasonably well established that preservation of ventricular contractility—within broad limits—is not demonstrably related to outcome. Dr. Reves's comments actually support the concept that such drugs as potent narcotics that do preserve ventricular contractility do not produce a measureable difference in outcome as compared to the inhalation agents, which are very potent *depressors* of ventricular contractility. The anesthesia literature is filled with documentation of myocardial depression by anesthetic agents and implications that this depression is bad and outcome-related. There are no data to support the outcome implications.

I believe it is unrealistic, and certainly bad public relations for our specialty, to continue the assertion that things such as preservation of ventricular contractility, as attractive as this is, are related to outcome—unless and until such is shown to be true.

In the meantime we should cease claiming superiority of one anesthetic regimen or drug based on such unproven concepts. Although it is true that multiinstitutional studies and large patient-outcome studies are very difficult and perhaps expensive, it seems inescapable that this is the bottom line we really have to know. To pretend that individual and more easily discovered and measured phenomena relate to outcome is penny wise and pound foolish, not only for our specialty but for all of medicine, and therefore for society in general.

William K. Hamilton, MD
Department of Anesthesia
University of California Medical Center
San Francisco, California 94143

Currency Scores, Medians, and Half-Lives

To the Editor:

In 1978, Pittinger published a procedure for evaluating currentness of biomedical textbooks (1). Designated by "currency scores," currentness calculated as follows:

$$\text{Currency Score} = \frac{1000}{\text{Copyright Date} - \text{Vintage Index.}}$$

The vintage index is the cube root of the product of mean, median, and mode for dates of all cited references characterized by author(s), title, volume, pagination, and date. These parameters of central tendency are derived from a statistical array of dates tabulated at annual intervals, and the vintage index was determined from these. This aspect of the derivation of a currency score was admittedly a long and tedious procedure.

In the course of analyzing a larger group of textbooks it became apparent that median and vintage index values were quantitatively similar. Indeed, the mean (± SD) for 65 medians was 1961.1 ± 11.1 and that for the vintage indexes was 1961.0 ± 11.2 ($r = >0.99$). In view of these similarities, we propose a simplified derivation for currency score:

$$\text{Currency Score} = \frac{1000}{\text{Copyright Date} - \text{Median.}}$$

Another related index of currentness is the half-life. The Journal Citation Reports of Science Citation Index defines half-life as "the number of journal publication years from the current year *back* whose articles have accounted for 50% of the total citations received in a given year" (2). Derivation of the half-life of a textbook is a simple procedure after the median has been determined, i.e.,

$$\text{Half-Life} = \text{Copyright Date} - \text{Median} + 1$$

Thus for a text with a copyright date of 1984 and a median of 1976.7, the half-life would be 1984 minus 1976.7 plus 1, or 8.3 years. A value of "1" (year) is added to the equation to compensate for Garfield's inclusion of the copyright year in the Science Citation Index methodology. It should be noted that all reference years below the median in the total distribution of dates relate to currency score, and all those above the median pertain to half-life.

Finally, it becomes apparent that

$$\text{Half-Life} = \frac{1000}{\text{Currency Score}} + 1$$

Charles B. Pittinger, MD
Vanderbilt University
Nashville, TN 37232

Edwin S. Munson, MD
University of Kentucky
Lexington, KY 40536

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Cost of Muscle Relaxant Drugs: Other Factors to Be Considered

To the Editor:

Aldrete et al. (Anesth Analg 1985;64:943–4) bring up an interesting point about muscle relaxant drugs (MRDs): the cost. Because there are differences in the duration of action in the older and newer MRDs and the relatively rapid rate of recovery from the new MRDs, other factors also need to be considered. Often in anesthesia practice, we have short operations that require muscle relaxation. If, at the conclusion of the operation, the patient's respiration is inadequate due to residual effects of MRDs, then the cost of additional operating room time, the cost of a respirator (starting at $32.00, followed by $4.00 for each extra hour), and the cost of being in the recovery room ($50.00 for each half hour) or the intensive care unit ($400.00 or more per day) may be many times more than the cost of the new MRDs. We should also consider the cost of the equipment needed for the intravenous infusion of succinylcholine (approximately $6.50) and the prices of anticholinesterases ($3.20 for a 10-ml vial of neostigmine), and anticholinergic drugs ($0.65 per ml of glycopyrrolate). It is, however, always justifiable to purchase a neuromuscular blockade monitor and its electrodes, regardless of which muscle relaxant drug is used. Finally, it is our goal to continue to research new drugs that will be more beneficial to the patients in addition to being cost effective.

Dung Q. Tran, MD
Anesthesia Section, Clinical Center
National Institutes of Health
Bethesda, MD 20892

Postanesthetic Theophylline Elimination[1]

To the Editor:

In an earlier communication, one of us (KN) reported that theophylline elimination was strongly inhibited during halothane anesthesia and was inhibited to a lesser degree during enflurane anesthesia (1). As the effect of halothane was to increase the apparent half-life of theophylline by 230%, we raised the question as to whether halothane might also interfere with theophylline elimination in the post-anesthetic phase during which some halothane would still be present. The data presented in Table 1 indicate that the effect of preexposure to halothane anesthesia does not have a statistically significant effect on theophylline elimination in the period 30–360 min after terminating halothane administration.

Table 1. Effect of Preexposure to Halothane on Theophylline Elimination in Dogs

	Control	Halothane
k_e (min^{-1})	0.0033	0.0026
	(0.0008)	(0.0005)
$t_{\frac{1}{2}}$ (min)	208	266

Anesthesia was induced with thiopental (35 mg/kg) and then maintained with halothane or no further anesthetic in the controls. Halothane was administered between 1 and 2% for 60 min, then stopped. Thirty minutes after stopping halothane administration, theophylline (10 mg/kg) was infused and venous blood samples were taken for theophylline analysis. Serum theophylline concentrations were measured by high performance liquid chromatography (2) for calculation of the elimination rate constant (k_e) and the apparent half-life ($t_{\frac{1}{2}}$). Values are given as the mean ± standard deviation, and a *t*-test for paired data was used to test for statistical significance.

$n = 5, P = 0.11$

Our previous finding of halothane inhibition of theophylline elimination was made under conditions that would have resulted in the high tissue concentrations of halothane, whereas the present observations were made under conditions that would have resulted in much lower tissue halothane concentrations. These results would be consistent with halothane acting as a competitive substrate for the enzymes that metabolize theophylline, and a diminution of effect as the concentration of halothane decreased.

Kanji Nakatsu, PhD
Christopher W. Loomis, PhD
Department of Pharmacology and Toxicology and the
Department of Anaesthesiology
Queen's University
Kingston, Ontario K7L 3N6
Canada

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Hepatic Blood Flow During Controlled Hypotension

Letter to the Editor:

The study by Sivarajan et al. (1) is mainly focused on changes in cerebral and coronary blood flows induced by controlled hypotension. However, a relatively long part of the discussion is devoted to changes observed in hepatic blood flow. The authors conclude that hepatic blood flow is not significantly impaired by hypotension induced with sodium nitroprusside or trimethaphan during halothane anesthesia. The conclusion is based on the absence of significant changes in total liver blood flow calculated as a sum of hepatic artery and portal vein blood flows. Total liver blood flow is one of the main determinants of liver function; however, liver oxygen supply per se is also important to liver function. Liver oxygen supply is determined to a large extent by an arterial fraction of total liver blood flow or, in other words, by hepatic arterial blood flow (HABF) rather than by total liver blood flow (2). Therefore, it is worth noting that in some studies HABF increased (3,4), or at least did not decrease (5,6), during nitroprusside-induced controlled hypotension (not exceeding a 35% decrease in blood pressure), and increased only temporarily (7) or decreased with trimethaphan (8). An increase in HABF during nitroprusside may result from preserved HABF autoregulation (an ability of HABF to increase in response to a decrease in portal blood flow) or from a pure vasodilating effect on

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[1] Supported by grants from the Medical Research Council of Canada and Anaquest.

Table 1. Blood Flow to the Liver (ml·100 g liver^{-1}·min^{-1})

	Control	Nitroprusside	Control	Trimethaphan
Hepatic artery blood flow	38 ± 7	43 ± 7	32 ± 4	34 ± 3
Total blood flow to liver	171 ± 20	190 ± 17	163 ± 10	140 ± 9
Ratio of hepatic artery blood flow and total blood flow to liver	0.22 ± 0.04	0.23 ± 0.03	0.2 ± 0.02	0.25 ± 0.02

hepatic arterial vasculature. Trimethaphan might have different effects on these mechanisms. If the authors (1) presented changes in HABF induced by both drugs (they do have the data), it could be of great value and provide the necessary information as to whether two hypotensive drugs are actually equally dangerous or safe for the liver in conditions of halothane anesthesia. On the other hand, similar effects of both hypotensive drugs on liver circulation (HABF to total hepatic blood flow ratio) in this study may reflect the influence of halothane rather than the hypotensive drug because halothane distorts HABF autoregulation to a greater degree than some other anesthetics (9).

Simon Gelman, MD, PhD
Department of Anesthesiology
University of Alabama at Birmingham
Birmingham, AL 35294

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In Response:

In our report (1) total blood flow to the liver, calculated as the sum of hepatic artery and portal vein flows, was normalized to the weight of abdominal viscera (gastrointestinal tract, pancreas, spleen, and liver) and should have been appropriately labeled "splanchnic blood flow." In response to Dr. Gelman's letter we present both hepatic artery blood flow and total blood flow to the liver in ml of blood·100 g of liver^{-1}·minute^{-1}, and the ratio of these two flows (mean ± SEM) (Table 1).

There were no significant differences when changes produced by each drug were compared to control values obtained before infusion of that drug, nor were there differences when changes from control produced by nitroprusside were compared to changes from control produced by trimethaphan. Our conclusion remains essentially the same, namely that hepatic blood flow is not significantly impaired by hypotension induced using nitroprusside or trimethaphan during halothane anesthesia.

Murali Sivarajan, MD
Department of Anaesthesiology
Kasturba Medical College
Manipal 576119
India

Reference

1. Sivarajan M, Amory DW, McKenzie SM. Regional blood flows during induced hypotension produced by nitroprusside or trimethaphan in the rhesus monkey. Anesth Analg 1985;64:759–66.

Uterine Displacement Device

To the Editor:

I read with interest the article by Endler and Donath describing an inflation device to prevent aortocaval compression (1). We have successfully utilized a similar device for more than two years. Our device, commercially available (Air Uterine Displacer (AUD), Flexguide Division Scientific Sales International Inc., PO Box 867 Ravina Station, Highland Park, IL 60035), differs from Endler's and Donath's device in two important aspects. First, the source of positive pressure for inflation of the bag placed under the right hip is simpler and always available to the anesthesiologist at no extra cost, that is the anesthesia machine. The bag is attached to the outlet of the anesthesia machine by a tubing and a male connector similar to that of the endotracheal tube. Inflation of the bag is achieved in a few seconds by pushing the oxygen flush valve. Then, by turning a two-way stop-cock, the required pressure is retained in the bag and monitored by an attached manometer. The bag is inflated to the optimum level prior to the induction of general anesthesia and immediately after the patient acquires the supine position with subarachnoid or epidural anesthesia, thus freeing the anesthesia machine for administering anesthesia or oxygen to the patient. Second, the bag we use is a disposable plastic one to eliminate the possibility of transmitting infection from one patient to the other through blood, amniotic fluid, or the skin. This may be an important medicolegal issue in view of the recent concern about nosocomial infections such as herpes, hepatitis, and AIDS.

Ezzat Abouleish, MD
Anesthesiology Department
The University of Texas at Houston
Houston, TX 77030

Reference

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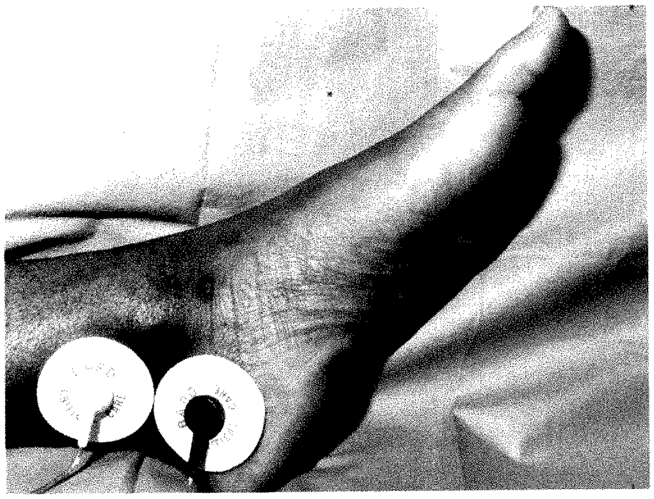

Figure 1. Electrode placement for neuromuscular assessment utilizing the posterior tibial nerve shown before twitch stimulation.

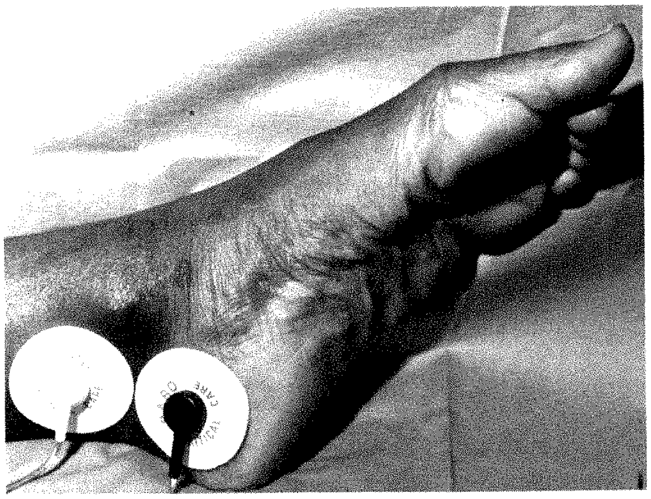

Figure 2. Electrode placement for neuromuscular assessment utilizing the posterior tibial nerve shown during twitch stimulation.

But Where Will I Put My Twitch Monitor?

To the Editor:

In this day of multiple surgical procedures and unique patient positions, it is not unusual for the anesthesiologist to find the patient lost amongst the drapes and operative fields. In fact, the anesthesiologist may paradoxically end up at the foot of the table and be heard to lament, "But where will I put my twitch monitor?" Conventional wisdom (or convenient tradition) results in the use of only the ulnar nerve–abductor pollicis brevis muscle or, if push comes to shove from the other side of the surgical drapes, the facial nerve–orbicularis oculi muscle (1), with the hope that the nerve is truly being stimulated (2).

I wish to remind the anesthesia community of a more convenient and reliable motor nerve that can be the appropriate solution when there is a problem of where to put the twitch monitor: the posterior tibial nerve. This nerve is just inferior and posterior to the medial malleolus and can even be "rolled" there like the ulnar nerve at the elbow. I simply place the electrodes inferior and posterior to the medial malleolus (Fig. 1) and stimulate the posterior tibial nerve, which causes plantar flexion of the toes (Fig. 2).

After working with scores of nurse anesthetists, anesthesia residents, and attending anesthesiologists in several different areas of the country, I have never seen this technique used. Yet it is convenient and reliable and, once demonstrated, never forgotten. Now we need never be without a place for our twitch monitors.

Lawrence P. Frank, MD
Department of Anesthesiology
University of Florida College of Medicine
Gainesville, Florida 32610-0254

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Book Reviews

Handbook of Physiology, Section 3: The Respiratory System. Volume I. Circulation and Nonrespiratory Functions

A. P. Fishman and A. B. Fisher, eds. Bethesda, MD: American Physiology Society, 1985, 572 pp, $136.00

The purpose of this series of handbooks is to provide a comprehensive view of contemporary respiratory physiology. This is not a textbook written for students, but a critical appraisal of current knowledge combined with a detailed discussion of controversies, written by authors who are research specialists in their respective topics.

The series has been outstanding in the past, and this volume maintains the high caliber of its contributions. Perhaps most noticeable is the extraordinary breadth of topics that are now considered functions of the lung; few of the topics contained in this volume were included in earlier editions. Control of breathing, lung mechanics, and gas exchange are topics to be covered by succeeding volumes in the series; and the present volume is devoted primarily to the biology of the lung in the broadest sense. Lung development, metabolic activity, regulation of circulating humoral agent, and the cellular interactions of hemostasis are the principal topics. Although they are disparate in subject matter, their presentation in a single volume conveys an extraordinary sense of how molecular biology, pathology, biochemistry, and physiology are drawing together to give a real basis for the understanding of the lung's function as an organ.

This is not to suggest that all is solved. On the contrary, a primary value of this book is the clear statement of the problems that remain. For the most part, the chapters review research in areas that have only recently been successfully pursued in the lung. Therefore each topic reveals as much about what needs to be done as it does about what is known. For a balanced summary of specialized areas of knowledge, this book is excellent, and the bibliography is selective but extensive for each chapter.

The first chapter, by P. Burri, focuses on the development and growth of the human lung. The second, by E. Weibel, discusses lung cell biology. They demonstrate nicely why knowledge of the lung has increased so rapidly and so far from the traditional functional confines of gas exchange. Both of these chapters are filled with exquisite electron microphotographs, and the structure revealed is correlated with function. The complexity of the changes that occur during development in the same species is revealed to be much more than a function of scale, and the stage is thereby set for subsequent chapters that explore some of the details of organ and cellular function in the lung.

A chapter by A. P. Fishman on the pulmonary circulation begins with a more traditional discussion of the passive forces responsible for distributing blood flow through the lung, but then proceeds to discuss the newer controversies on the active regulation of blood flow, the causes of pulmonary hypertension, and the importance of the bronchial circulation. Lung water balance and the occurrence of pulmonary edema is discussed thoroughly in an erudite chapter by A. E. Taylor and J. C. Parker.

The chapters on lung metabolism are introduced by one on oxygen utilization and toxicity in the lungs, by A. B. Fisher and H. J. Forman. This chapter is an outstanding example of the value of this book, for it brings together material from many sources to demonstrate the bioenergetics of the lung and the special mechanisms developed for the high oxygen environment of the lung cells that can be homeostatic or pathogenic. Subsequent chapters on glucose metabolism, by D. F. Tierney and S. L. Young, protein metabolism, by D. Massaro, and lipid synthesis, by R. J. King and J. A. Clements confirm the depth of knowledge being accumulated.

The next four chapters discuss humoral materials that are regulated by or synthesized by lung tissues. These chapters on 5-hydroxytryptamine, angiotensin, and eicosanoids are interesting; the one by M. Hamosh and F. Hamosh on lipoproteins and lipoprotein lipase is particularly stimulating.

The final four chapters all concern functions more directly related to pathology. Macrophages in the respiratory tract are discussed by J. D. Brain, the importance of cilia by P. Satir and E. R. Dirksen, blood coagulation by R. W. Colman and A. Z. Budzynski, and the interaction between platelets and the blood vessel wall by R. Ross and S. M. Schwartz. The last two chapters are particularly relevant to the pathophysiology of systemic disease because it is finally becoming clear that the basis for the apparent paradox that the initiating events of coagulation may not be the same as those determining hemostasis lies in the process of cell-to-cell communication. The significance of this has barely been appreciated in clinical practice, and therefore it is a fitting conclusion to an exciting, innovative, and information-packed volume.

In general, the chapters are well-written and well-illus-

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trated. If a concise but thorough and critical treatment of one or all of these topics is required for the researcher or clinician, a better source would be hard to find.

Only one general criticism seems warranted, and that is that three years appear to have elapsed between the preparation of the manuscripts and their publication. For such active fields of investigation, this is an inordinately long time. Nevertheless, this is a book that will be stimulating to all who are seriously interested in the basis of function and pathophysiology in the lung.

Bryan E. Marshall, MD, FRCP,
Horatio C. Wood Professor of Anesthesia
Director, McNeil Center for Research in Anesthesia
University of Pennsylvania
Philadelphia, PA 19104

Pulmonary Development, Transition from Intrauterine to Extrauterine Life

G. H. Nelson, ed. New York: Marcel Dekker, Inc., 1985, 536 pp, $70.00 (US and Canada), $90.00 (all other countries).

This book is Volume 27 in the series entitled "Lung Biology in Health and Disease" (Claude Lenfant, ed.). The general content of this book includes abnormal pulmonary function in genetically normal premature infants. The book has been organized to present in a temporal way pulmonary maturation from early lung development in utero to long-term follow-up of survivors of respiratory distress syndrome.

The first four chapters are concentrated in the basic sciences and include early prenatal development of the human respiratory system, the morphology of lung development, the developmental biochemistry of lung surfactant, and fetal breathing activity. The next part focuses on the obstetrician's evaluation of the fetus by amniocentesis, amniotic fluid analysis, and amniotic fluid lecithin concentrations. There is a section focusing on the factors influencing pulmonary maturity such as diet (deficiency of palmitic acid), maternal drugs, and maternal–fetal disorders. There are discussions of the modern maternal transport system, the use of tocolytics, the instillation of surfactant into the trachea, and a review of neonatal resuscitation.

The neonatal intensive care unit is then described, with reference to perinatal regionalization and a general survey of all the respiratory distress syndromes seen in the neonate. Separate chapters are given both to the survivors and nonsurvivors of respiratory distress syndrome, with special reference to the pathology of bronchopulmonary dysplasia and long term consequences on somatic growth and the central nervous system.

The final chapter offers a look into the future summarizing the various authors' views of their specialty areas. Considering all aspects, the book is quite interesting and thought-provoking. However, it is more oriented to the obstetrician, perinatalogist, and/or the neonatalogist. In spite of the many authors, Dr. Nelson has edited well, avoiding any repetition, and the list of references at the end of each chapter is exceptionally complete. On the negative side is the fact that seven of nineteen chapters are authored by faculty from one institution, thus presenting a parochial view of the subject. The obstetrical and/or pediatric anesthesiologist might find this book more informative and useful than the anesthesia resident or the general anesthesiologist. For the person desiring a review of the current state of the art of lung development from fetus to newborn, this treatise should suffice.

John G. Shutack, DO
Assistant Professor of Anesthesiology and Pediatrics
Hahnemann University
Philadelphia, PA 19102

Monitoring in Anesthesia and Critical Care Medicine

C. D. Blitt, ed. New York: Churchill Livingstone, 1985, 740 pp, $79.00.

A new book on a familiar topic is always faced with justifying its existence, especially when established texts of acknowledged quality with up-to-date information and lower cost are available. Does *Monitoring in Anesthesia and Critical Care Medicine* meet the test and justify itself as a current, high-quality tome with an equal or superior position to existing books on monitoring?

Monitoring in Anesthesia and Critical Care Medicine is an authoritative work in which a large number of current and clinically relevant monitoring issues are discussed. The authorship of each chapter reflects the high caliber of the contributors, many of whom are acknowledged experts in their field. Perhaps the strongest praise of this book is the fact that most of its chapters have the ability to stand alone, providing extensive considerations of their topics. The chapter by Dr. Vandam, "The Senses As Monitors," is particularly noteworthy for its ability to survey years of experience watching the exponential growth of monitoring technology, yet still being able to find an indispensable place in today's world for the individual, the anesthesiologist, in the clinically beneficial coupling of patient and hardware.

Although the individual authors and their considerations of individual topics goes a long way toward establishing a place on the shelf for this new book, the conglomerate structure of the text is confusing. The title of the book suggests that it has considered monitoring both in and out of the operating room, perhaps under major headings of preanesthetic, intraoperative, recovery, and intensive care settings. This is not the case. These phases are explored, but in a nonuniform and segregated fashion throughout various chapters. In certain cases, little or no consideration is given to perianesthetic monitoring methods. An example of this is the sparse information provided on preanesthetic or intraoperative use of radionuclide and echocardiographic monitoring of the cardiovascular system. Another neglected topic is intensive care unit clinical monitoring of the adequacy of respiratory function essential for establishing criteria for endotracheal extubation.

The structure selected for this book is an organ systems approach followed by an applications section to specific anesthetic subspecialties. Priority has been given to cardiovascular, respiratory, and neurosensory monitoring. Four hundred and forty-seven pages (61 percent of the text) are devoted to these topics. Part of the reason for the larger than necessary number of pages devoted to these areas is that topics related but not specific to monitoring are included. Pharmacologic therapy of dysrhythmias, for example, is well discussed in the chapter on "Electrocardiographic Monitoring." The question that needs answering, however, is the appropriateness of pharmacologic therapy in a text on monitoring.

The separation of an organ system and its clinical application seems artificial and repetitious. The chapter on "Monitoring In Cardiac Anesthesia," for example, neatly summarizes much of the material in the chapters from the section on "Monitoring the Cardiovascular System." Blending this material into one, rather than two separated sections, might have been a more efficient and effective way to present the information. Even within the same major heading, considerable repetition is obvious. Cannulation sites, for example, are discussed in both the chapter on "Central Venous Pressure Monitoring" and the chapter on "Pulmonary Artery Catheterization." Mass spectrometry is another example, present in "Monitoring Anesthetic and Respiratory Gases" and "Monitoring the Anesthetic Delivery System."

All other monitoring apart from cardiovascular, respiratory, and neurosensory is included in the section headed "Miscellaneous Monitoring." This judgmental relegation of temperature, renal, electrolyte, coagulation, anesthetic delivery system, and neuromuscular monitoring to the "Miscellaneous" category may be misdirected emphasis. Only 98 pages (13 percent of the text) are devoted to all of these important topics. A similar situation exists in the "Monitoring and Subspecialties" section, where pediatric, obstetric, and outpatient monitoring is reviewed in only 87 pages (12 percent of the text). Although the chapter on evoked potential monitoring is important and very well presented, does it deserve to be 9 percent of a general reference text? Why is there little or no information provided on monitoring in the recovery room, the intensive care unit, or on related topics such as acquisition and maintenance of monitoring equipment and electrical and occupational safety?

The editor's preface to *Monitoring in Anesthesia and Critical Care Medicine* states several reasons for writing this new text on a familiar topic. First stated is "the need . . . for a complete, state-of-the-art text on monitoring." This new text considers its subject well but doesn't completely replace existing books. As for being "state-of-the-art," this is almost impossible for a book, several years in the writing, about a field in which the technology is changing every few months. Though published in 1985, even this book has scant information on pulse oximetry, for example, which has recently become a standard, almost essential monitoring method. The most up-to-date information about monitoring can be provided to the reader only in a frequently published, looseleaf format, rather than an infrequently published bound text. A second reason mentioned for writing this text is to provide information "on monitoring, with an emphasis on the fields of anesthesia and critical care medicine." Yet as stated earlier, the second half of this aim (surveying monitoring and critical care medicine) has not been fully realized.

The last reason provided by the editor for having written this new book is to have it serve as "a general reference on monitoring and as such . . . [differ] . . . from other publications on the subject of monitoring." Although it does not differ from other monitoring texts, it is a good, current, general reference. For that reason, the answer to this reviewer's original question, does this text justify its own existence, is basically affirmative. At present, the most appropriate shelf for this volume is that in a reference library. A recommendation to change the location to a shelf in everyone's personal library will require the next edition of this text to be streamlined, consolidated, less narrow in its topical considerations, and more competitively priced.

Alan Jay Schwartz, MD, MSEd
Associate Professor of Anesthesia
Hospital of the University of Pennsylvania and
The Children's Hospital of Philadelphia
Philadelphia, PA 19104

Labat's Regional Anesthesia, Techniques and Clinical Applications (4th ed.)

John Adriani, ed. St. Louis: Warren H. Green, Inc., 1985, 744 pp, $75.00.

> . . . the general opinion is erroneous which considers the practice of regional anesthesia to mean simply the accomplishment of a few injections, or the administration of a few ounces of anesthetic solution to a patient who cannot take ether.

So wrote Gaston Labat in 1922 in a "General Discussion on the Value of Regional Anesthesia," a chapter in the first edition of his landmark text. A condensation of the author's collective experience of thousands of cases, its object was to promote rapid acquisition of a working knowledge of regional anesthetic techniques. Written for surgeons, it was the first comprehensive book on the subject. Chapters were organized by body area, with description of block techniques following a brief anatomical review. Extensive discussion of theory was intentionally omitted. After being out of print for more than thirty years, the text was revived in 1967 by John Adriani, who was well-suited to the task, given his many contributions to the field and his training as a study at Bellevue with Labat's protégé, Wertheim. Adriani has preserved Labat's format, the exceptional diagrams and plates, and much of the original text.

A burgeoning interest in regional anesthesia over the last two decades has prompted publication of numerous texts and revival of the American Society for Regional Anesthesia. Into this climate Adriani has introduced a fourth edition of Labat, newly available after a hiatus of thirteen years. Inherent in this task was a dual challenge: how to preserve the flavor of a classic, yet ensure its viability as a reference of more than historical import? The solution is a composite of Labat's original, augmented by knowledge of physiology, pharmacology, and anesthetic methods new since the last printing.

When compared to its predecessor, there is much familiar information in this edition. Two new chapters, "Topical Anesthesia" and "Early History and Foundations of Regional Anesthesia," are appended to the unchanged order of the first seventeen. The latter retain much of their 1967 text and the character of Labat's original, with noteworthy additions and revisions. Discussion of method in chapter one mentions the role of preservatives in the allergic response to local anesthetics and the suitability of regional techniques for ambulatory surgery. A completely revamped section on drugs for regional anesthesia follows, expanded to include mechanisms of action, physicochemical characteristics, and the spectrum of drug allergy. Updated references include the author's work on local anesthetic toxicity and allergy.

Practical instruction in blocks of cranial, spinal, and autonomic nerves are vintage Labat. Adriani has modernized the phraseology for today's reader and incorporated newer techniques, such as the perivascular approach to the brachial plexus, refined by Alon Winnie. The chapter on spinal anesthesia was authored in 1967 by Adriani to replace the outmoded material in earlier editions; it is minimally changed here by a discussion of spinal anatomy and inclusion of lidocaine and bupivacaine into the armamentarium with older agents dibucaine, procaine, and tetracaine. The rising popularity of epidural anesthesia has prompted an expanded discussion of anatomic considerations, current drugs, saline and blood patches, and complications of the technique. A token paragraph on intraspinal narcotics in this chapter discusses the intrathecal route of administration only. Commentary on the kinetics of opioids in the CSF and on their side effects is totally absent. Topical anesthesia, the oldest regional technique, merits a new chapter, the depth and detail of which make it a useful, quick reference for both anesthesiologists and surgeons.

A fitting close for the book is the retrospective chapter on the origins and development of regional anesthesia. Landmark discoveries, contested "firsts" in the chronology, and stories that over the decades have become legendary provide pleasurable reading. Enjoyment of this section is somewhat marred, however, by frequent (and sometimes flagrant) typographical errors. All the new material incorporated into this edition suffers for want of vigorous proofreading. This, and the lack of updated bibliographic references, constitute its most obvious shortcomings.

Where Labat once stood alone, he is now joined on the bookshelf by multiple volumes in the expanding field of regional anesthesia. None today can claim to be encyclopedic, but this forebear is unequalled in its clarity of explanation and impeccable illustrations. As such, it remains the Baedecker of block books, a reliable guide to the goal best described in Labat's final paragraphs, 1922:

> The practice of regional anesthesia is an art. It requires special knowledge of anatomy, skill in the performance of its various procedures, experience in the method of handling patients, and gentleness in the execution of surgical procedures.

Andrea M. Baldeck, MD
Assistant Professor of Anesthesia
University of Pennsylvania
Philadelphia, PA 19104

Classical Anesthesia Files

David M. Little Jr. Park Ridge, IL: Wood Library-Museum of Anesthesiology, 1985, 335 pp, $35.00.

For me, one of the highlights of *Survey of Anesthesiology* has always been its Classical File, a regular feature since the journal's 1957 inception, conducted by Dr. David Little until his death in 1981. It consisted of a classic article, along with Little's erudite, witty commentary, written in an elegant and graceful style. Clearly others feel the same, for those 150 commentaries and landmark articles (the latter in abridged form) have been collected and published in one volume by the Wood Library-Museum of Anesthesiology.

As stated in the preface, "Dr. Little culled medical literature from the 18th century through the 1960s for seminal papers which led to landmark changes in the evolution of anesthesiology. Identifying these important contributions was only the beginning. What evoked genuine awe of Dr. Little's achievements was his originality of concept, breadth of treatment, and depth of knowledge apparent in each of his introductory comments preceding each reprint of an historical contribution. His clear flowing style of a storyteller transformed his pleasure in writing to pleasure in reading."

This is so; pick any of his comments and see. For example, on the importance of curare in anesthetic practice: "No longer was it necessary to employ deep and toxic levels of general anesthesia in the hope that, like a shotgun blast, the pellets of the single agent would strike all the various physiologic systems of the body necessary in order to provide the essential facets of general anesthesia . . ." Or on premedication: "If the patient could reply to 'good afternoon' when he was wheeled into the operating room suite, he immediately received . . . morphine and . . . scopolamine intravenously on the spot!"

The book is arranged chronologically by classic article, beginning in 1775 with Priestly and Lavoisier; through Long, Morton, Jackson, and Wells; and ending with the 1967 publication of the National Halothane Study and the first clinical report on pancuronium. It is a walk through anesthetic history conducted by a master. Surely it ranks with Stanley

Sykes's *Essays* as a most felicitous book that gives satisfaction and pleasure and knowledge each time it is picked up.

Lee H. Cooperman
Professor of Anesthesia
University of Pennsylvania School of Medicine
Philadelphia, PA 19103

1985 Yearbook of Critical Care Medicine

M. Rogers, et al. Chicago: Yearbook Medical Publishers, 1985, 493 pp, $42.95.

This text is the third in the annual Yearbook series of Critical Care Medicine. The *1985 Yearbook of Critical Care Medicine* is edited by Mark Rogers, MD, in conjunction with six members of the Johns Hopkins University School of Medicine faculty. The book provides a condensed summary of articles relevant to critical care medicine, along with a critique of each article reviewed. As noted in the introduction to this book, critical care medicine crosses traditional departmental lines. Accordingly, the literature relevant to the field can be found in journals representing numerous disciplines of medicine. The *1985 Yearbook of Critical Care Medicine* reviews 324 articles from 91 journals representing several countries.

The text is divided into 14 sections covering a broad scope of topics ranging from shock and trauma to socioeconomic and ethical issues. The articles cover both basic science investigation and clinical studies, including case reports. The most comprehensive section deals with cerebral hemodynamics. Subjects covered in this section include cerebral protection, pharmacologic interventions, effect and management of increased intracranial pressure, cerebral blood flow, and cerebral metabolism. In general, the sections are well-balanced and will be useful to any physician involved in the care of critically ill patients. However, the section on operative monitoring will be particularly useful to the clinical anesthesiologist, whereas the section on nutritional considerations will be of interest primarily to anesthesiologists and other physicians involved in the ongoing care of critically ill patients.

The summaries are concise and easy to read. The editors' comments are generally scholarly, pertinent, and clinically applicable. The book is an excellent review of the current state of the art and science in the management of critically ill patients. Anesthesiologists will find the material in this book very useful in caring for critically ill patients, both in the operating suite and in intensive care units.

Morris Brown, MD
Assistant Professor of Anesthesiology
Wayne State University School of Medicine
Director, Critical Care Services
Sinai Hospital of Detroit
Detroit, MI 48235

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A Guide for Authors

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Nicholas M. Greene, MD
Editor in Chief
Anesthesia and Analgesia
Yale University School of Medicine
333 Cedar Street, New Haven, CT 06510

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Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," reprinted in *Annals of Internal Medicine* 1982;96:766-71 and *Lancet* 1982;284:1766-70.

Use the checklist given below for preparation of manuscripts:

General

- ☐ Original articles describe in 3000 words or less clinical or laboratory investigations.
- ☐ Clinical reports describe in 1000 words or less either new and instructive case reports or anesthetic techniques and equipment of demonstrable originality, usefulness, and safety.
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- ☐ Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, should be on a separate page), and legends. Type only on one side of the paper and number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.
- ☐ Submit three copies of manuscript and figures in a heavy paper envelope. Submitted manuscripts should be accompanied by a covering letter, and permissions to reproduce previously published materials or to use illustrations that may identify subjects.
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Books and Other Monographs:

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   Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974:406.
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11. *Agency Publication*
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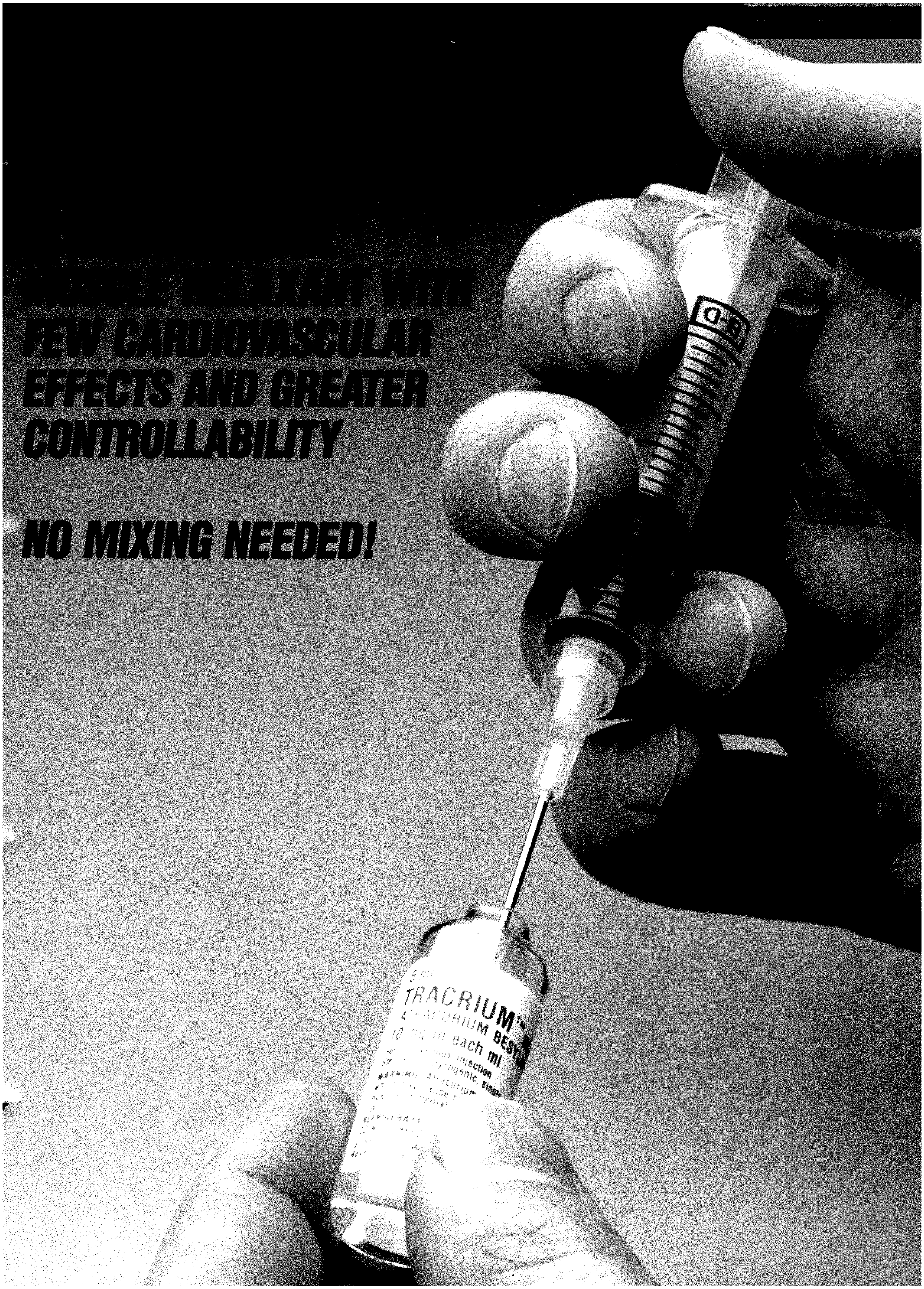
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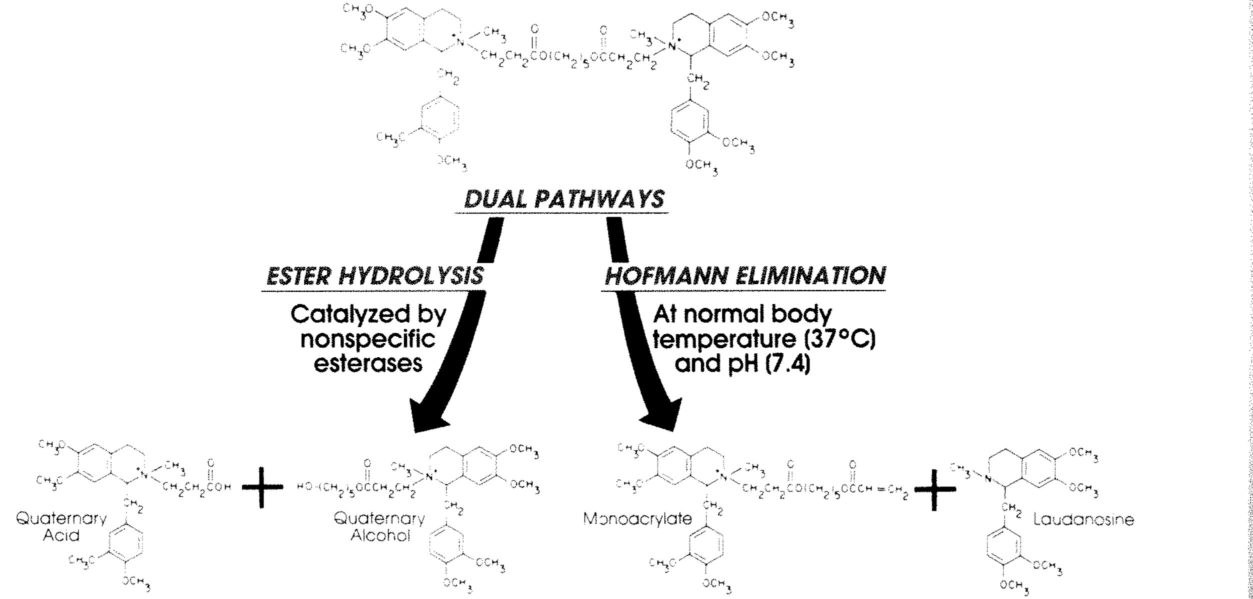

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1 *Hofmann elimination—a nonenzymatic process that occurs at physiologic temperature and pH*

2 *Ester hydrolysis—catalyzed by nonspecific esterases; normal levels of plasma cholinesterase are not required*

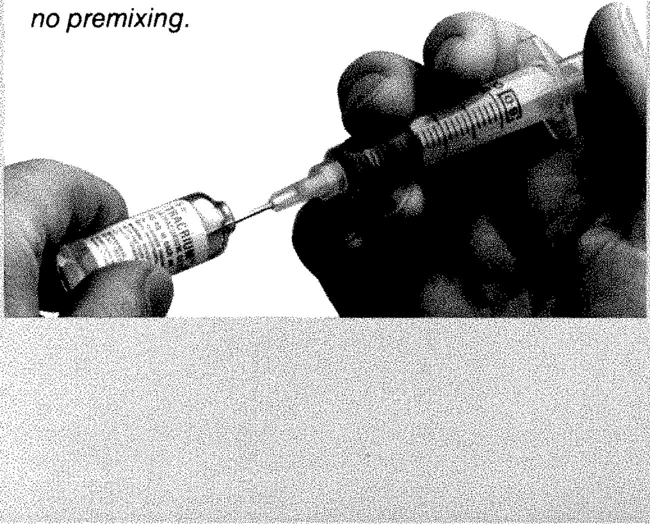
These attributes make Tracrium a more flexible surgical muscle relaxant—it may be tailored to a wide variety of surgical cases.

"Atracurium has the special feature of being broken down to inactive products by the Hofmann elimination reaction. This means that the active drug can be removed from the biophase by other means not totally dependent on enzyme action, redistribution or excretion."[1]

"At present, no other available muscle relaxant undergoes this kind of degradation at physiologic pH."[2]

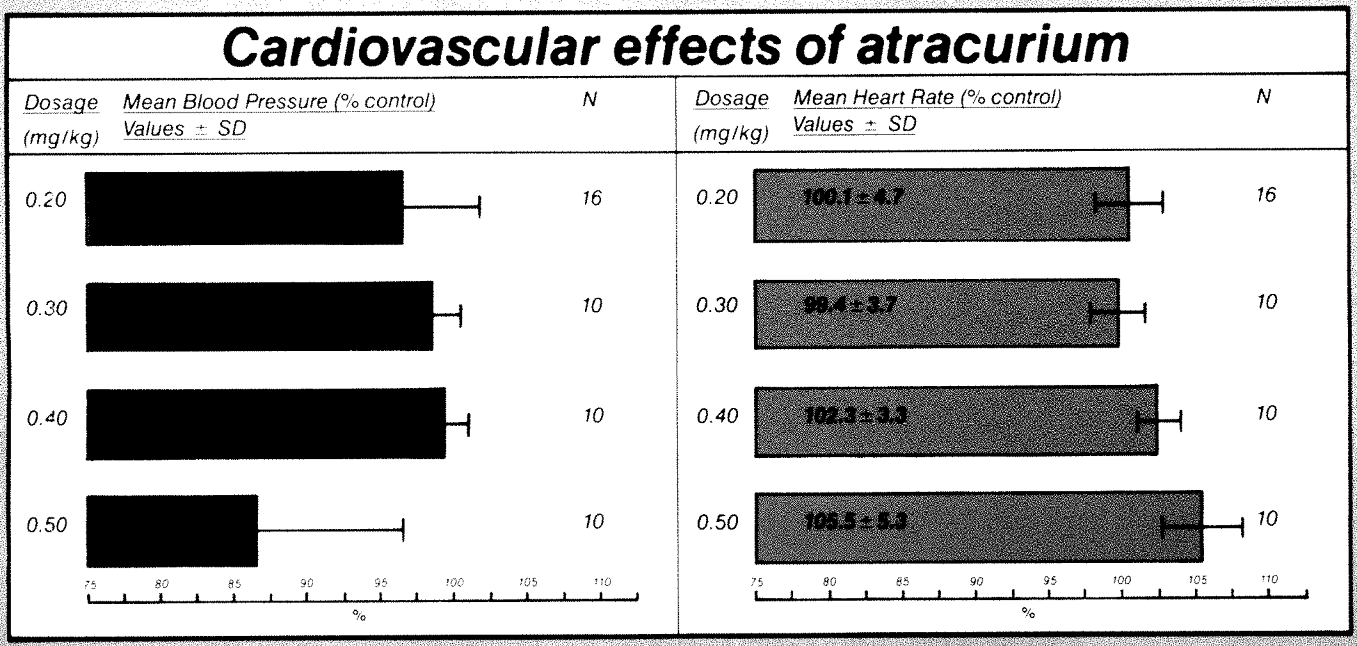
Convenient and Ready to Use

Tracrium is easily administered—requires no premixing.



Few Cardiovascular Effects at Recommended Dosages

☐ *Tracrium* (atracurium besylate) produces virtually no clinically significant cardiovascular hemodynamic changes when administered at recommended dosage levels—a significant benefit in patients with compromised cardiac ability or cardiac risk.*



Adapted from Basta et al.[3]

No Cumulative Effects Upon Recovery, After Multiple Doses

☐ *Repeated equipotent doses of Tracrium, administered at equal points of recovery, have no cumulative effect on recovery time*

☐ *Once recovery begins, it is relatively rapid and independent of dose*

☐ *This means that you do not have to calculate progressively smaller doses for repeat administration, and that recovery is more consistent and predictable*

"One patient received 12 successive doses of atracurium after recovering completely from the initial dose, yet the 25%-75% recovery times were 10.0 and 12.2 min, respectively. This may indicate that atracurium is not cumulative...."[1]

Minimal Histamine Release

☐ *Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine*

☐ *Clinically significant histamine release occurs well within the clinical dosage range (at ED_{95}) for curare, at the upper limits of the clinical dosage range (at 2 × ED_{95}) for metocurine and outside the clinical dosage range (at 3 × ED_{95}) for atracurium*[4]

☐ *The lack of hemodynamic changes due to Tracrium suggests minimal histamine release*

Please see brief summary of prescribing information on the following page.

REFERENCES:

1. *Ali HH, Savarese JJ, Basta SJ, et al: Clinical pharmacology of atracurium: A new intermediate acting nondepolarizing relaxant.* Seminars in Anesthesia *1982; 1:57-62.*
2. *Katz RL, Stirt J, Murray AL, et al: Neuromuscular effects of atracurium in man.* Anesth Analg *1982; 61:730-734.*
3. *Basta SJ, Ali HH, Savarese JJ, et al: Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscle relaxant.* Anesth Analg *1982; 61:723-729.*
4. *Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, and d-tubocurarine.* Anesthesiology *1982;57:A261.*

TRACRIUM® INJECTION
(atracurium besylate)

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TRACRIUM® INJECTION
(atracurium besylate)

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

DESCRIPTION: Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:

General: Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine. The possibility of substantial histamine release in sensitive individuals must be considered however. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

NEW!
10 ml Multi-Dose Vial
now available for
TRACRIUM® INJECTION
(atracurium besylate)

- **Convenient**
- **Economical**
- **Uniquely Identifiable**

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. Atracurium was evaluated in a battery of three short term mutagenicity tests. It was non-mutagenic in both the Ames Salmonella assay at concentrations up to 1000 μg/plate, and in a rat bone marrow cytogenicity assay at up to paralyzing doses. A positive response was observed in the mouse lymphoma assay under conditions (80 and 100 μg/ml, in the absence of metabolic activation) which killed over 80% of the treated cells; there was no mutagenicity at 60 μg/ml and lower, concentrations which killed up to half of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations (1200 μg/ml and higher) which also killed over 80% of the treated cells. Mutagenicity testing is intended to simulate chronic (years to lifetime) exposure in an effort to determine potential carcinogenicity. Thus, a single positive mutagenicity response for a drug used infrequently and/or briefly is of questionable clinical relevance.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 2 years have not been established.

ADVERSE REACTIONS: Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

Approximately one million patients received Tracrium during the first year following introduction to the U.S. market in December, 1983. Spontaneously reported adverse reactions were uncommon (approximately 0.02%). The following adverse reactions are among those most frequently reported, but there are insufficient data to support an estimate of their incidence:

Musculoskeletal: Inadequate block, prolonged block
Cardiovascular: Hypotension, vasodilatation (flushing), tachycardia, bradycardia
Respiratory: Dyspnea, bronchospasm, laryngospasm
Integumentary: Rash, urticaria, reaction at injection site

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended following the use of succinylcholine for intubation under balanced anesthesia.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for patients with significant cardiovascular disease and for patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated.

No Tracrium dosage adjustments are required for patients with renal disease or for pediatric patients two years of age or older. In pediatric patients, maintenance doses may be required with slightly greater frequency than in adults.

HOW SUPPLIED: Tracrium Injection, 10 mg atracurium besylate in each ml. Ampuls of 5 ml (50 mg atracurium besylate per ampul). Box of 10 ampuls (NDC-0081-0940-10).

10 ml Multiple Dose Vial (100 mg atracurium besylate per vial). The multiple dose vial contains 0.9% benzyl alcohol added as a preservative. Box of 10 (NDC-0081-0940-95).

Store under refrigeration at 2° to 8°C (36° to 46°F); DO NOT FREEZE.

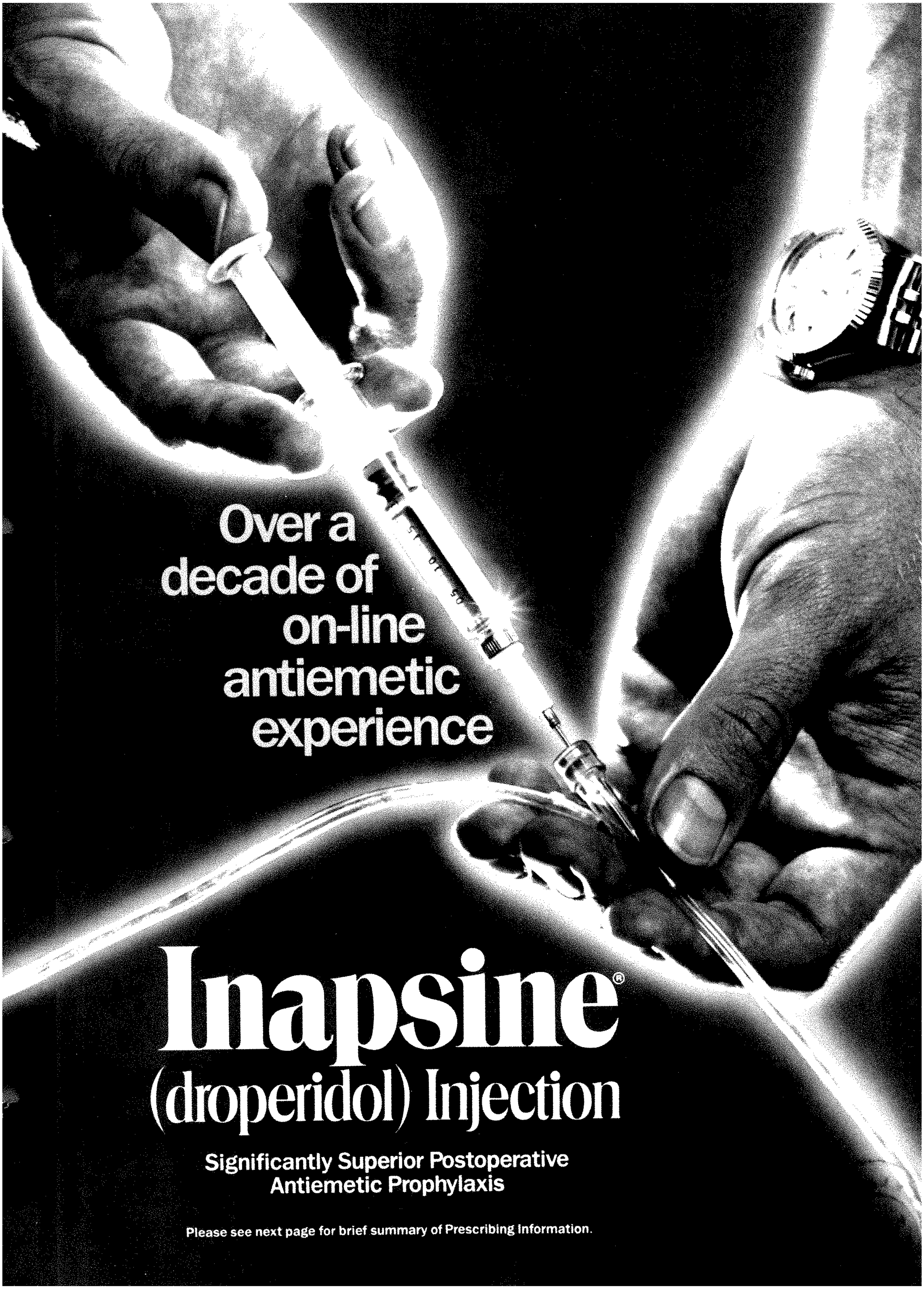
U.S. Patent No. 4179507

Printed in U.S.A.

TRACRIUM® INJECTION
(atracurium besylate)

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

85TRA11



Over a decade of on-line antiemetic experience

Inapsine®

(droperidol) Injection

Significantly Superior Postoperative Antiemetic Prophylaxis

Please see next page for brief summary of Prescribing Information.

Over a decade of on-line antiemetic experience

- Proven in double-blind studies to provide postoperative antiemetic effect (when given perioperatively) that is significantly superior to placebo,[1,2] diazepam[2] and hydroxyzine[2,3]
- Potent antiemetic activity extends through discharge from recovery room
- May be administered *intraoperatively* in long procedures as well as preoperatively in both long and short procedures
- Helps maintain cardiovascular stability by protecting against hypertensive episodes, heart rate changes and the pressor and arrhythmogenic effects of epinephrine
- Facilitates a comfortable, anxiety-free emergence, reducing the need for postoperative opioids

Inapsine®
(droperidol) Injection

Significantly Superior Postoperative Antiemetic Prophylaxis

Before prescribing please consult complete prescribing information, of which the following is a brief summary.
Protect from light. Store at room temperature.
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY.
Droperidol is a neuroleptic (tranquilizer) agent.

DESCRIPTION: *2 ml. and 5 ml. ampoules:* Each ml. contains Droperidol 2.5 mg. and lactic acid for pH adjustment to 3.4 ± 0.4
10 ml. vials: Each ml. contains Droperidol 2.5 mg. with 1.8 mg. methylparaben and 0.2 mg. propylparaben, and lactic acid for pH adjustment to 3.4 ± 0.4

INDICATIONS: INAPSINE (droperidol) is indicated: • to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures; • for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia; • in neuroleptanalgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE* (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE.
As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.

If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.

PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms, INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.

Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effect with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias. (See full prescribing information for complete description.)

ADVERSE REACTIONS: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).

When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur; if these remain untreated, respiratory arrest could occur.

Elevated blood pressure, with or without pre-existing hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely

Usual Adult Dosage

I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.

II. Adjunct to General Anesthesia
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

If INNOVAR* injection is administered in addition to INAPSINE (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Insert for full prescribing information.

III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml.) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.

IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

How Supplied: *2 ml. and 5 ml. ampoules*—packages of 10;
10 ml. multiple-dose vials—packages of 10.
U.S. Patent No. 3,161,645
NDC 50458-010-02; NDC 50458-010-05; NDC 50458-010-10
March 1980, Revised June 1980 IP41C98-M

Manufactured by TAYLOR PHARMACAL CO. for

JANSSEN
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Janssen Pharmaceutica Inc., Piscataway, New Jersey 08854

REFERENCES: 1. Patton CM Jr, Moon MR, Dannemiller FJ: The prophylactic antiemetic effect of droperidol. *Anesth Anal* 1974;53:361-364
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3. Mehta P, Theriot E, Mehrotra D, et al: Comparative evaluation of preanesthetic medications. *Curr Ther Res* 1984;35:715-720.

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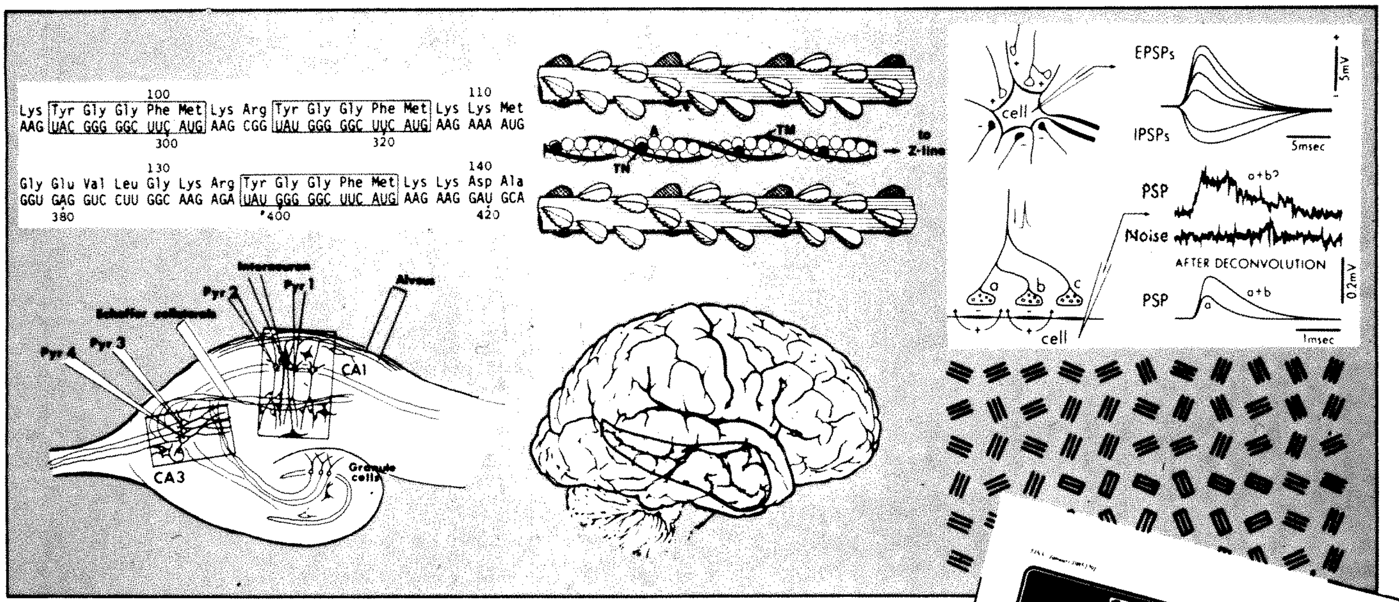
Trends in NeuroSciences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Interneuron
Pyr 2
Pyr 1
Alveus
Schaffer collaterals
Pyr 4
Pyr 3
CA1
CA3
Granule cells
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IPSPs
5mV
5msec
PSP
a+b?
Noise
AFTER DECONVOLUTION
a+b
0.2mV
a
b
c
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From genes to behaviour –the central connection

This is probably the most exciting time to be working in neuroscience. At last it seems as though many of the secrets of the nervous system are yielding to research. The genes for the acetylcholine receptor, the sodium channel and the three opioid peptide precursors have all been cloned. The crucial role of molecular genetics within neuroscience is firmly established.

The new technology has demonstrated the ability of a handful of gene products to orchestrate a complex sequence of behaviour in the marine mollusc *Aplysia*. Rapid progress is also being made in understanding how specific gene products control development in the insect's nervous system, or regulate the switching of transmitter production in adult mammalian neurons. Undoubtably molecular genetics will have a major impact on clinical neuroscience during the 1980s.

A special subscription rate 30% below the personal subscription is available for all students (undergraduate, graduate, postgraduate) and neurology residents. The 1986 student subscription rate is UK £21.00; USA and Canada US$37.00; Europe 98.00 Dutch Guilders; Rest of World 107.00 Dutch Guilders. Student subscriptions must be accomplished by valid proof of student status.

Gene research in neuroscience is not the only area where activities are occuring at an explosive rate. PET studies of human cognitive function, computer monitoring of whole body and limb movement and psychophysical testing of perceptual activities are all contributing to our knowledge of higher brain functions in health and disease.

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Albumin & PPF are no safer or more effective than Hespan®

(hetastarch)

...they're simply

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As safe as albumin or PPF

In comparative clinical studies, platelet counts, hematocrits, serum fibrinogen levels, prothrombin times (PT), and partial thromboplastin times (PTT) seen with Hespan were comparable to those seen with albumin or plasma protein fraction (PPF).[1,2]

Other studies demonstrate that when any reduction in platelet count or prolongation of PT or PTT does occur with Hespan, no increased bleeding results, even in patients with multiple trauma.[3-5] As with any volume expander, patients should be monitored for excessive hemodilution of coagulant factors or circulatory overload when large volumes are administered.

When Hespan-treated patients were monitored to detect localized or systemic sepsis, there was no evidence of a decrease in their ability to ward off infection or combat an established infection.[5]

Hespan is nonantigenic and, as with blood-derived colloids, any risk of allergic reaction is minimal. Hespan also has a negligible effect on subsequent blood typing or crossmatching.[6]

As effective as albumin or PPF

Comparative clinical studies have repeatedly demonstrated that Hespan is as effective as albumin or PPF in postoperative myocardial revascularization,[1-3] and hemorrhagic, traumatic, or septic shock.[4,5,7]

No significant differences between Hespan and albumin or PPF were noted in any efficacy parameter.[1-5,7] Hespan effectively maintained colloid osmotic pressure, restored plasma volume, and improved cardiac output and renal function in hypovolemic patients.[1-5,7] And, the volume-expanding effect of a single infusion of Hespan can persist for 24 hours or longer.

Half the price of albumin or PPF

Hespan offers a potential savings to your hospital of tens of thousands of dollars a year.

double the price.

For additional information, contact the Medical Services Department, American Critical Care, 1600 Waukegan Road, McGaw Park, IL 60085. Phone 1-800-323-4980.

Lifesaving, moneysaving

HESPAN®
(hetastarch)

American Critical Care

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Please see references and brief summary of prescribing information on following page.

References: 1. Diehl JT, Lester JL, Cosgrove DM: Clinical comparison of hetastarch and albumin in postoperative cardiac patients. *Ann Thorac Surg 34* (6):674-679, 1982. **2.** Moggio RA, Rha CC, Somberg ED, et al: Hemodynamic comparison of albumin and hydroxyethyl starch in postoperative cardiac surgery patients. *Crit Care Med 11* (12):943-945, 1983. **3.** Kirklin JK, Lell WA, Kouchoukos NT: Hydroxyethyl starch versus albumin for colloid infusion following cardiopulmonary bypass in patients undergoing myocardial revascularization. *Ann Thorac Surg 37* (1):40-46, 1984. **4.** Puri VK, Paidipaty B, White L: Hydroxyethyl starch for resuscitation of patients with hypovolemia and shock. *Crit Care Med 9* (12):833-837, 1981. **5.** Shatney CH, Deepika K, Militello PR, et al: Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. *Arch Surg 118*:804-809, 1983. **6.** Daniels MJ, Strauss RG, Smith-Floss AM: Effects of hydroxyethyl starch on erythrocyte typing and blood crossmatching. *Transfusion 22* (3):226-228, 1982. **7.** Rackow EC, Falk JL, Fein IA, et al: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med 11*(11):839-850, 1983.

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CONTRAINDICATIONS

Hetastarch is contraindicated in patients with severe bleeding disorders or with severe congestive cardiac and renal failure with oliguria or anuria.

WARNINGS

Large volumes may alter the coagulation mechanism. Thus, administration of hetastarch may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of hetastarch.

Usage in Leukapheresis: Significant declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures due to the volume expanding effects of hetastarch. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by hetastarch and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values.

Usage in Pregnancy: Reproduction studies have been done in mice with no evidence of fetal damage. Relevance to humans is not known since hetastarch has not been given to pregnant women. Therefore, it should not be used in pregnant women, particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the potential hazards.

Usage in Children: No data available pertaining to use in children.

The safety and compatibility of additives have not been established.

PRECAUTIONS

The possibility of circulatory overload should be kept in mind. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Indirect bilirubin levels of 0.83 mg% (normal 0.0-0.7 mg%) have been reported in 2 out of 20 normal subjects who received multiple hetastarch infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering hetastarch to patients with a history of liver disease.

Regular and frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of hetastarch use during leukapheresis. Studies should include CBC, total leukocyte and platelet counts, leukocyte differential count, hemoglobin, hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT).

Hetastarch is nonantigenic. However, allergic or sensitivity reactions have been reported (see ADVERSE REACTIONS). If such reactions occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

ADVERSE REACTIONS

The following have been reported: vomiting, mild temperature elevation, chills, itching, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, and anaphylactoid reactions consisting of periorbital edema, urticaria, and wheezing.

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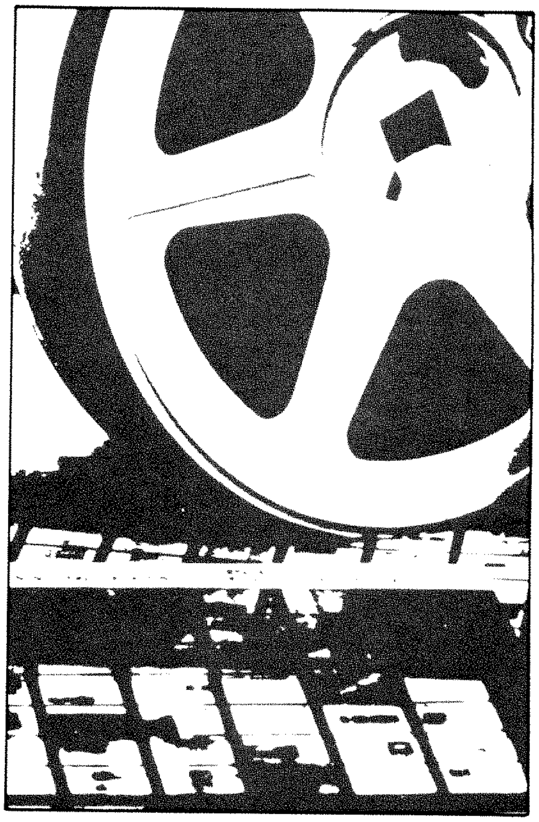

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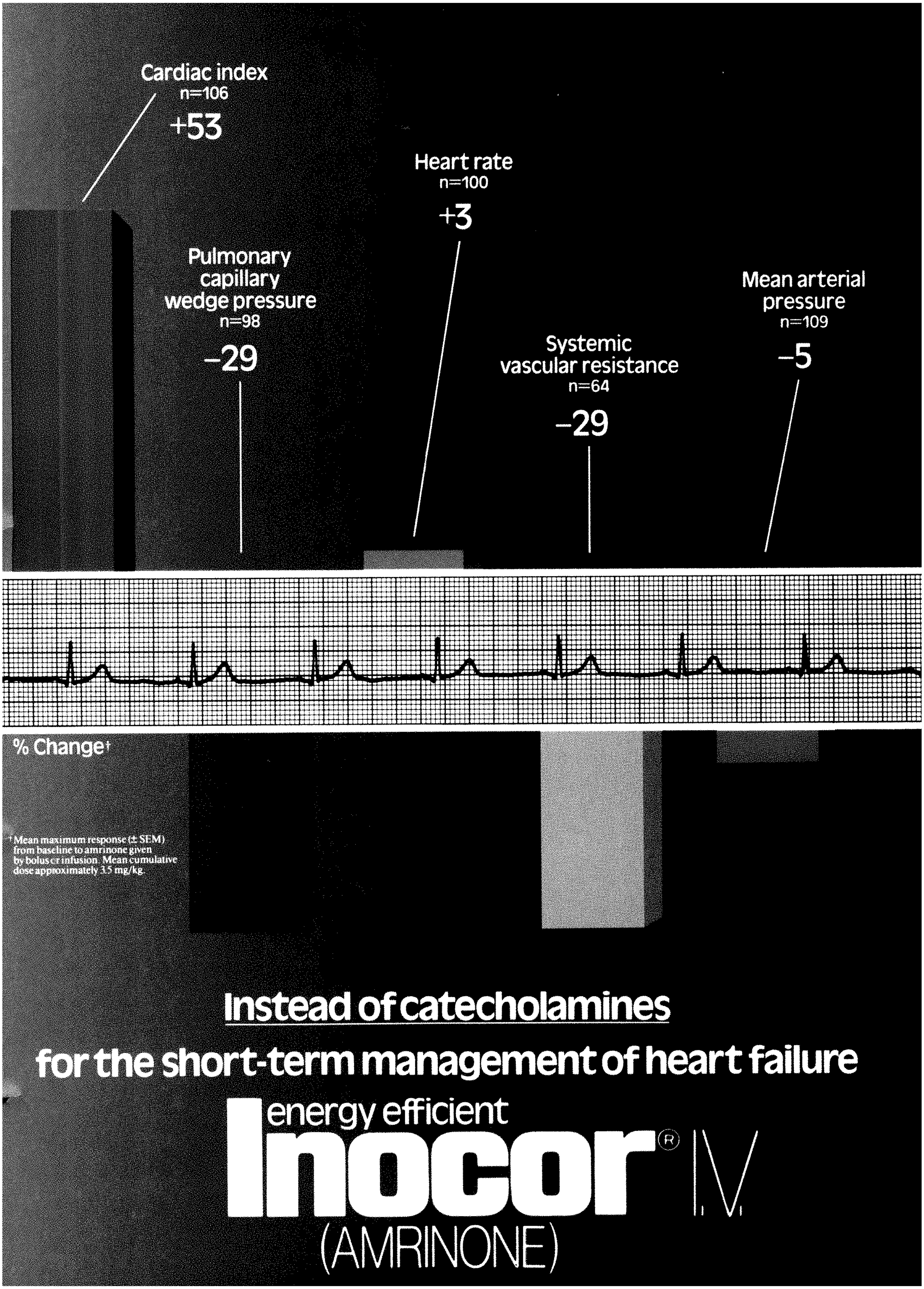

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Please see brief summary of product information on this page for contraindications, adverse reactions, patient selection, and precautionary recommendations.

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INOCOR lactate injection, brand of amrinone lactate, represents a new class of cardiac inotropic agents with vasodilator activity, distinct from digitalis glycosides or catecholamines.

INDICATIONS AND USAGE (INOCOR lactate injection is indicated for the short-term management of congestive heart failure in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators.)

INOCOR lactate injection is indicated for the short-term management of congestive heart failure. Because of limited experience and potential for serious adverse effects (see ADVERSE REACTIONS), INOCOR should be used only in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators. Although most patients have been studied hemodynamically for periods only up to 24 hours, some patients were studied for longer periods and demonstrated consistent hemodynamic and clinical effects. The duration of therapy should depend on patient responsiveness.

CONTRAINDICATIONS INOCOR lactate injection is contraindicated in patients who are hypersensitive to it.

It is also contraindicated in those patients known to be hypersensitive to bisulfites.

PRECAUTIONS *General:* INOCOR lactate injection should not be used in patients with severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

During intravenous therapy with INOCOR lactate injection, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients showing excessive decreases in blood pressure.

Patients who have received vigorous diuretic therapy may have insufficient cardiac filling pressure to respond adequately to INOCOR lactate injection, in which case cautious liberalization of fluid and electrolyte intake may be indicated.

Supraventricular and ventricular arrhythmias have been observed in the very high-risk population treated. While amrinone per se has not been shown to be arrhythmogenic, the potential for arrhythmia, present in congestive heart failure itself, may be increased by any drug or combination of drugs.

Thrombocytopenia and hepatotoxicity have been noted (see ADVERSE REACTIONS).

LABORATORY TESTS *Fluid and electrolytes:* Fluid and electrolyte changes and renal function should be carefully monitored during amrinone lactate therapy. Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalized patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

DRUG INTERACTIONS In a relatively limited experience, no untoward clinical manifestations have been observed in patients in whom INOCOR lactate injection was used concurrently with the following drugs: digitalis glycosides, lidocaine, quinidine, metoprolol, propranolol; hydralazine, prazosin, isosorbide dinitrate, nitroglycerine; chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, captopril, heparin, warfarin, potassium supplements, insulin, diazepam.

One case of excessive hypotension was reported when amrinone was used concurrently with disopyramide.

Until additional experience is available, concurrent administration with Norpace® disopyramide should be undertaken with caution.

USE IN ACUTE MYOCARDIAL INFARCTION INOCOR is not recommended for use in acute myocardial infarction.

USE IN CHILDREN Safety and effectiveness in children have not been established.

USE IN PREGNANCY *Pregnancy category C.* In New Zealand white rabbits, amrinone has been shown to reduce fetal skeletal and gross external malformations at oral doses of 16 mg/kg and 50 mg/kg that were toxic for the rabbit. Studies in French Hy/Cr rabbits using oral doses up to 32 mg/kg/day did not confirm this finding. No malformations were seen in rats receiving amrinone intravenously at the maximum dose used, 15 mg/kg/day (approximately the recommended daily IV dose for patients with congestive heart failure). There are no adequate and well-controlled studies in pregnant women. Amrinone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

USE IN NURSING MOTHERS Caution should be exercised when amrinone is administered to nursing women, since it is not known whether it is excreted in human milk.

ADVERSE REACTIONS *Thrombocytopenia.* Intravenous INOCOR lactate injection resulted in platelet count reductions to below 100,000/mm^3 in 2.4% of patients.

Gastrointestinal effects: Gastrointestinal adverse reactions reported with INOCOR lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdominal pain (0.4%), and anorexia (0.4%).

Cardiovascular effects: Cardiovascular adverse reactions reported with INOCOR lactate injection include arrhythmia (3%) and hypotension (1.3%).

Hepatic toxicity: In dogs, at IV doses between 9 mg/kg/day and 32 mg/kg/day, amrinone showed dose-related hepatotoxicity manifested either as enzyme elevation or hepatic cell necrosis or both. Hepatotoxicity has been observed in man following long-term oral dosing and has been observed, in a limited experience (0.2%), following IV administration of amrinone.

Hypersensitivity: There have been reports of several apparent hypersensitivity reactions in patients treated with oral amrinone for about two weeks. Signs and symptoms were variable but included pericarditis, pleuritis, and ascites (one case), myositis with interstitial shadowing on chest x-ray and elevated sedimentation rate (one case); and vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (one case). The first patient died, not necessarily of the possible reaction, while the last two resolved with discontinuation of therapy. None of the cases were rechallenged, so attribution to amrinone is not certain, but possible hypersensitivity reactions should be considered in any patient maintained for a prolonged period on amrinone.

General: Additional adverse reactions observed in intravenous amrinone clinical studies include fever (0.9%), chest pain (0.2%), and burning at the site of injection (0.2%).

OVERDOSAGE Doses of INOCOR lactate injection may produce hypotension because of its vasodilator effect. If this occurs, amrinone administration should be reduced or discontinued. No specific antidote is known, but general measures for circulatory support should be taken.

MANAGEMENT OF ADVERSE REACTIONS *Platelet count reductions:* Asymptomatic platelet count reduction (to less than 150,000/mm^3) may be reversed within one week of a decrease in drug dosage. Further, with no change in drug dosage, the count may stabilize at lower than predrug levels without any clinical sequelae. Predrug platelet counts and frequent platelet counts during therapy are recommended to assist in decisions regarding dosage modifications.

Should a platelet count less than 150,000/mm^3 occur, the following actions may be considered:

- Maintain total daily dose unchanged, since in some cases counts have either stabilized or returned to pretreatment levels.
- Decrease total daily dose.
- Discontinue amrinone if, in the clinical judgment of the physician, risk exceeds the potential benefit.

Gastrointestinal side effects: While gastrointestinal side effects were seen infrequently with IV therapy, should severe or debilitating ones occur, the physician may wish to reduce dosage or discontinue the drug based on the usual benefit-to-risk considerations.

Hepatic toxicity: In clinical experience to date with IV administration, hepatotoxicity has rarely been observed. If acute marked alterations in liver enzymes occur together with clinical symptoms, suggesting an idiosyncratic hypersensitivity reaction, amrinone therapy should be promptly discontinued.

If less than marked enzyme alterations occur without clinical symptoms, these nonspecific changes should be evaluated on an individual basis. The clinician may wish to continue amrinone and reduce the dosage or discontinue the drug based on the usual benefit-to-risk considerations.

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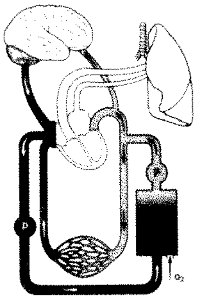

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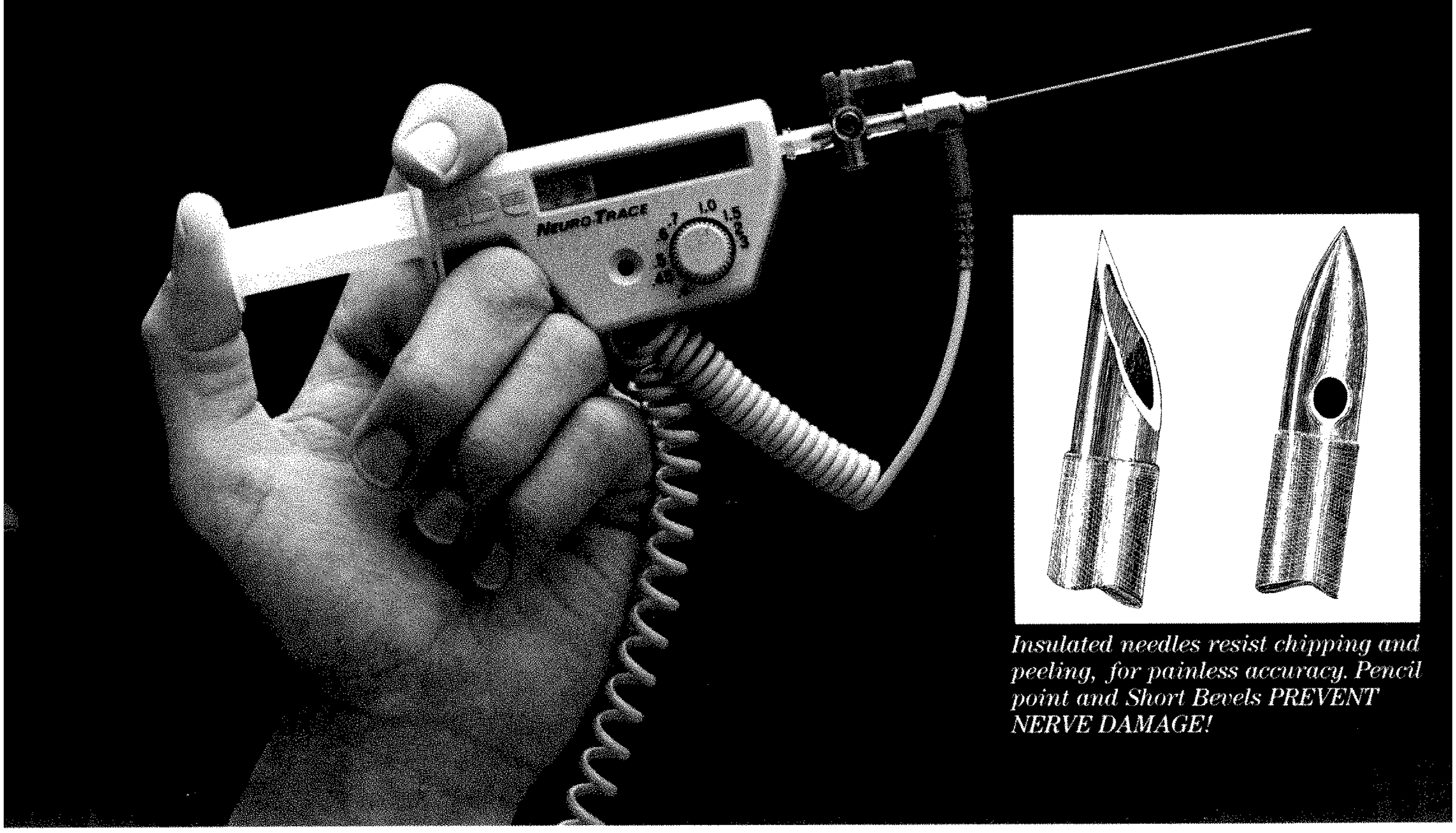

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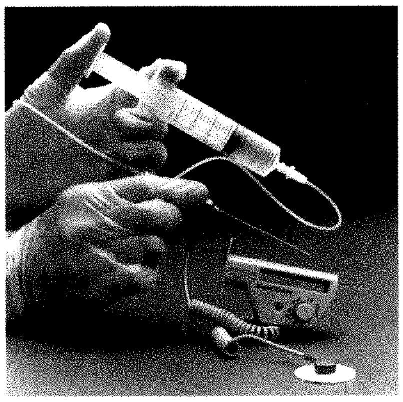

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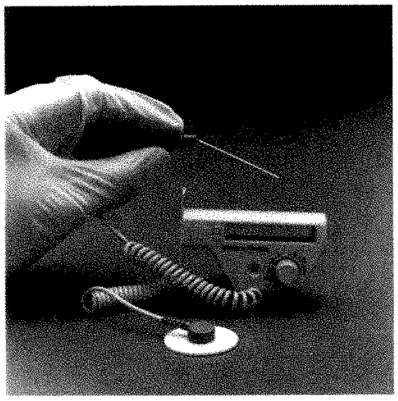

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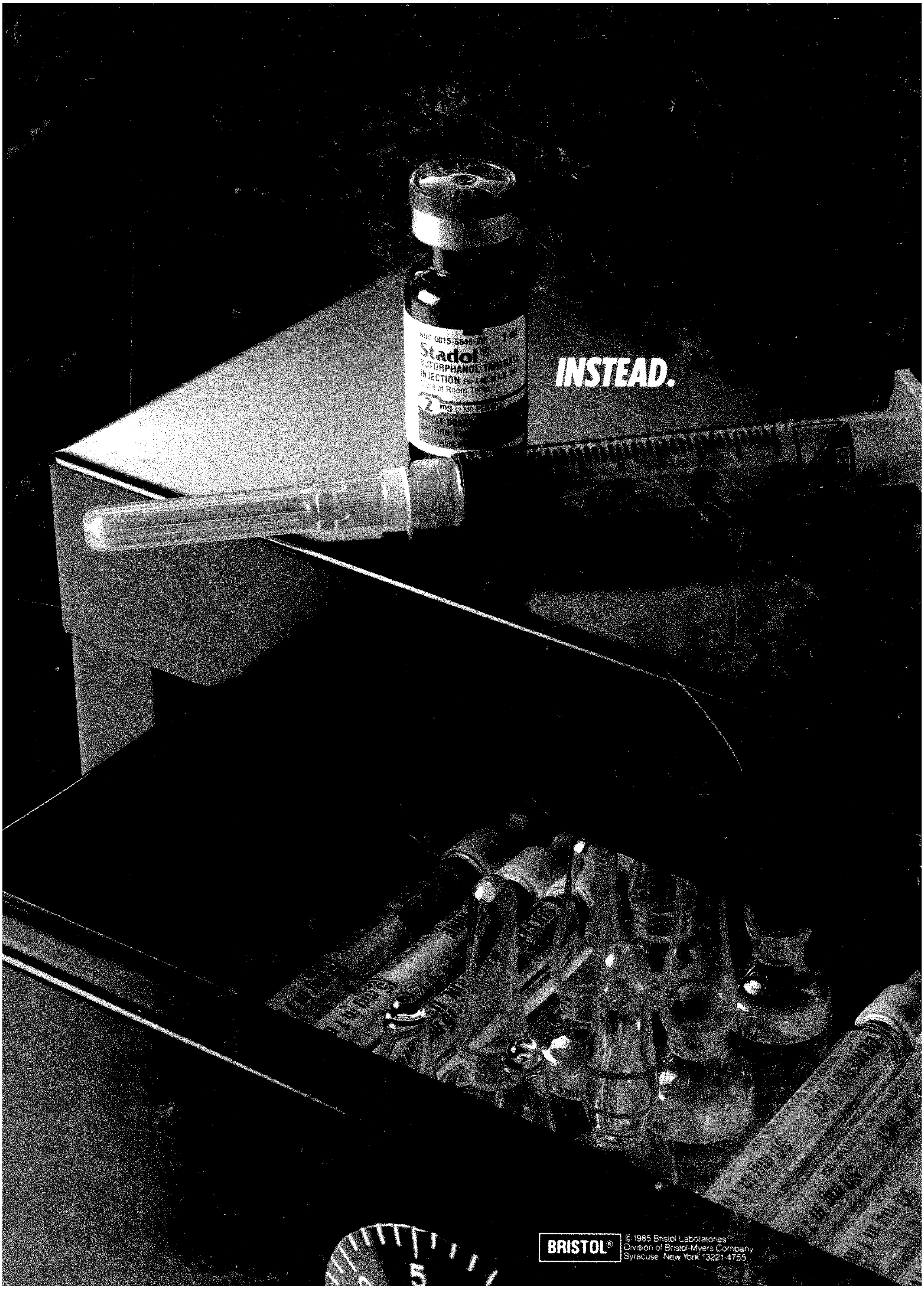

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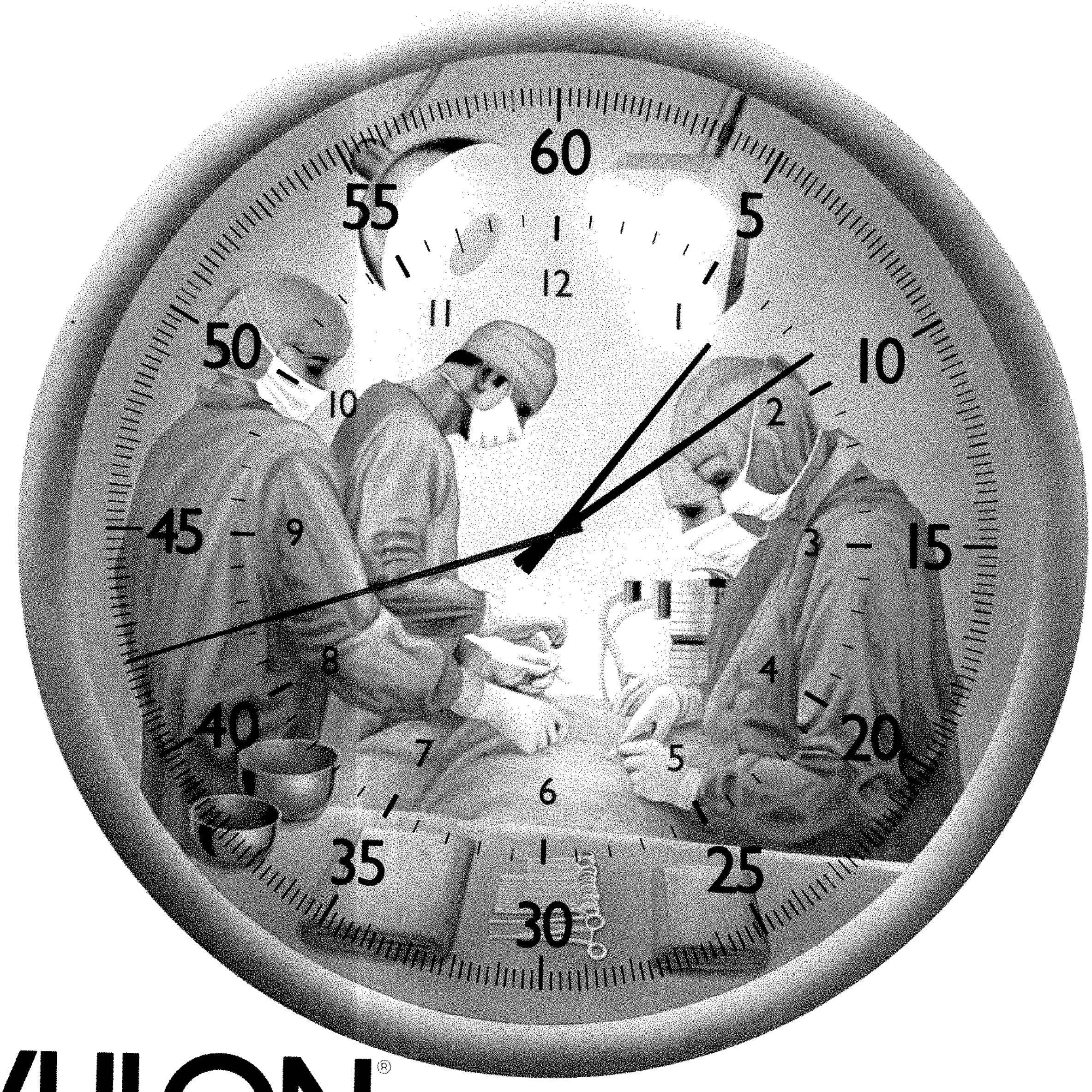

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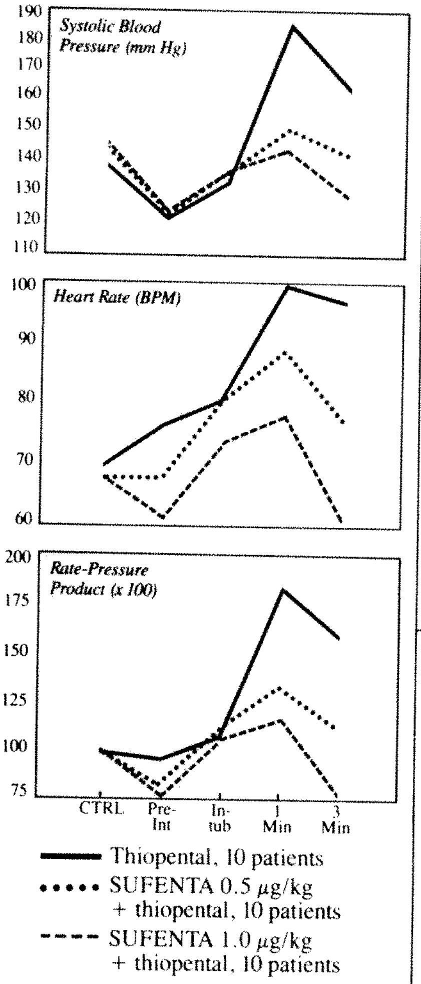
THE SUFENTA® REPORT
A PRACTICAL ANESTHESIA UPDATE
VOL. 1, NO. 1 JANSSEN PHARMACEUTICA INC. WINTER 1986

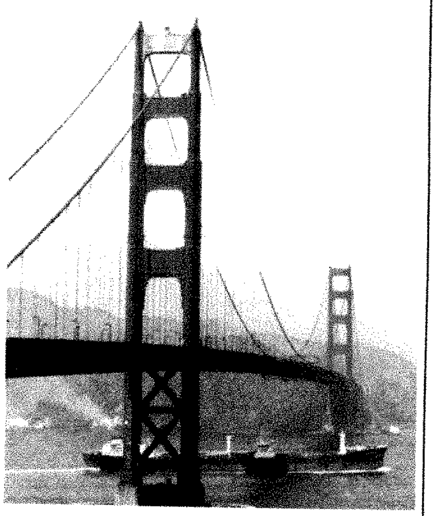
LESS BARBITURATE, BETTER STABILITY WITH LOW-DOSE SUFENTA®

SAN FRANCISCO: Low doses of SUFENTA® (sufentanil citrate) Injection ©,given prior to thiopental as an adjunct to induction, improved hemodynamic stability and reduced barbiturate requirements, according to a study presented here at the 1985 Annual Meeting of the A.S.A. In a group of 30 adult patients who underwent surgery of 25 min. to 8.5 hr. duration, thiopental was used for induction, either alone or combined with SUFENTA. SUFENTA (0.5 or 1.0 μg/kg) reduced thiopental requirements by 50% to 68%, respectively, and the hemodynamic response to laryngoscopy and intubation was attenuated, as measured by systolic pressure, heart rate and rate-pressure product. Bradycardia, truncal rigidity and recall were not observed.

Better Hemodynamic Control



(Abstracted from Brizgys, Morales and Owens, *Anesthesiology* 1985; 63:A377)



Experience With 93 Patients Generates "Thumbnail" Dosage Guidelines

Clinical experience with SUFENTA in general surgery revealed that *total dosage requirements averaged about 1 μg/kg/hour or less*, in surgery up to 8 hours.

In the same patients the *induction dose averaged about 75% of total dose.* The remainder was given in incremental maintenance doses as needed.

The induction dose of SUFENTA administered prior to intubation reduces hypertension and tachycardia.

In every case, however, dosage should be titrated to individual patient needs.

NOW SHOWING:
AN INFORMATIVE 22-MINUTE FILM

Benjamin J. Kripke, MD, and Edson O. Parker III, MD, are featured in the medical film "SUFENTA: A Practical Guide for General Surgical Procedures." The anesthesiologists demonstrate, through actual hands-on experience, how careful dosage planning provides maximal hemodynamic stability throughout the entire procedure. To arrange a viewing of this film, please contact your local Janssen Representative.

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Adult Dosage Recommendations: A Summary

Please see full Prescribing Information, including dosage, on next page.

	General Surgical Procedures	Major Surgical Procedures
Expected Duration	1 to 2 hours	2 to 8 hours
Types of Procedures	Total vaginal hysterectomy, gall bladder surgery, bilateral inguinal hernia repair, open reduction of fractures	Major orthopedic surgery, carotid endarterectomy, nephrectomy, major abdominal surgery (e.g., colectomy)
Recommended Induction Dose	1 to 1.5 μg/kg (1.4 to 2.1 ml for a 70 kg patient), administered with N_2O/O_2, endotracheal intubation and mechanical ventilation	1 to 5 μg/kg (1.4 to 7 ml for a 70 kg patient), administered with N_2O/O_2, endotracheal intubation and mechanical ventilation
Recommended Maintenance Dose	10 to 25 μg (0.2 to 0.5 ml) based upon changes in clinical signs and patient's response to initial dose	10 to 25 μg (0.2 to 0.5 ml) based upon changes in clinical signs and patient's response to initial dose
Total Dosage	For cases lasting 2 hours, would not be expected to exceed 2 μg/kg (2.8 ml for a 70 kg patient) when used with N_2O/O_2	For cases lasting 8 hours, would not be expected to exceed 8 μg/kg (11.2 ml for a 70 kg patient) when used with N_2O/O_2

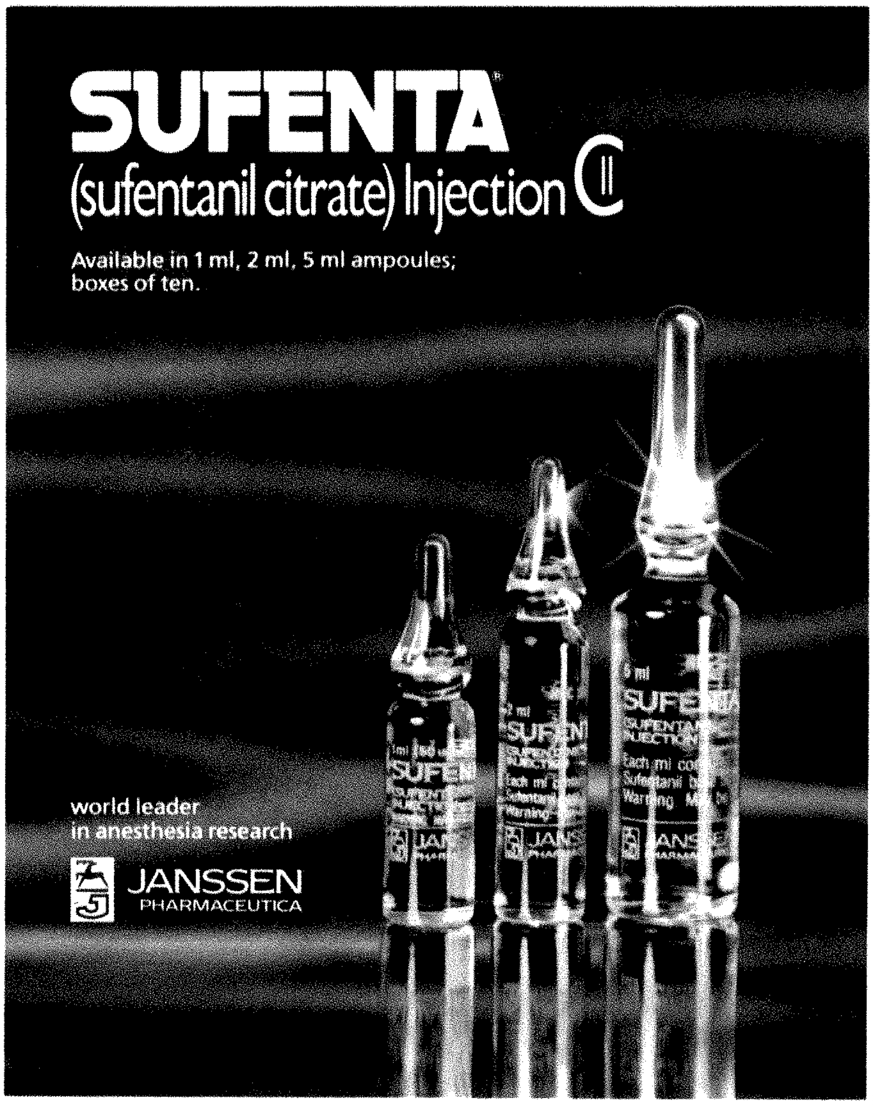
SUFENTA® BRIEFCASE

Putting SUFENTA to Work in Your Practice

In actual clinical practice, when used in balanced general anesthesia, SUFENTA is about 10 times as potent as fentanyl. Thus, 1 ml SUFENTA (50 μg/ml) is equivalent to 10 ml fentanyl (50 μg/ml).

Because of this potency difference, less volume of drug is needed, making it especially convenient for use in cardiovascular surgery and longer procedures. For accurate dosage calibration in shorter procedures, a tuberculin syringe, a 2 ml insulin syringe or dilution may be helpful.

In a laboratory study, SUFENTA has been found to be compatible and stable in solution with 5% glucose in water, 5% glucose in normal saline, lactated Ringer's solution and normal saline (tested in plastic containers refrigerated at 4°-8°C for 24 hours followed by 48 hours at room temperature).



SUFENTA®

(sufentanil citrate) Injection CII

Available in 1 ml, 2 ml, 5 ml ampoules; boxes of ten.

world leader in anesthesia research

JANSSEN PHARMACEUTICA

SUFENTA® (sufentanil citrate) Injection CII

CAUTION: Federal Law Prohibits Dispensing Without Prescription.

DESCRIPTION: SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

SUFENTA is a sterile, preservative free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-6.0.

CLINICAL PHARMACOLOGY: SUFENTA is an opioid analgesic. When used in balanced general anesthesia, SUFENTA has been reported to be as much as 10 times as potent as fentanyl. When administered as a primary anesthetic agent with 100% oxygen, SUFENTA is approximately 5 to 7 times as potent as fentanyl. (See dosage chart for more complete information on the use of SUFENTA.) At doses of up to 8 µg/kg, SUFENTA provides profound analgesia; at doses ≥8 µg/kg, SUFENTA produces a deep level of anesthesia. SUFENTA produces a dose related attenuation of catecholamine release, particularly norepinephrine.

The pharmacokinetics of SUFENTA can be described as a three-compartment model, with a distribution time of 1.4 minutes, redistribution of 17.1 minutes and an elimination half-life of 164 minutes. The liver and small intestine are the major sites of biotransformation. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug. Plasma protein binding of SUFENTA is approximately 92.5%.

SUFENTA has an immediate onset of action, with relatively limited accumulation. Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with equipotent dosages of fentanyl. At dosages of SUFENTA of 1-2 µg/kg, recovery times are comparable to those observed with fentanyl; at dosages of >2-6 µg/kg, recovery times are comparable to enflurane, isoflurane and fentanyl. Within the anesthetic dosage range of 8-30 µg/kg of SUFENTA, recovery times are more rapid compared to equipotent fentanyl dosages.

At dosages of ≥8 µg/kg, SUFENTA produces hypnosis and anesthesia without the use of additional anesthetic agents. A deep level of anesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to 25 µg/kg attenuate the sympathetic response to surgical stress. The catecholamine response, particularly norepinephrine, is further attenuated at doses of SUFENTA of 25-30 µg/kg, with hemodynamic stability and preservation of favorable myocardial oxygen balance.

The vagolytic effects of pancuronium may produce a dose dependent elevation in heart rate during SUFENTA-oxygen anesthesia. The vagolytic effect of pancuronium may be reduced in patients administered nitrous oxide with SUFENTA. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent may be used to maintain a stable lower heart rate and blood pressure during SUFENTA-oxygen anesthesia.

Preliminary data suggest that in patients administered high doses of SUFENTA, initial dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane.

Bradycardia is infrequently seen in patients administered SUFENTA-oxygen anesthesia. The use of nitrous oxide with high doses of SUFENTA may decrease mean arterial pressure, heart rate and cardiac output.

Assays of histamine in patients administered SUFENTA have shown no elevation in plasma histamine levels and no indication of histamine release.

SUFENTA at 20 µg/kg has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anesthesia supplementation in one study of patients undergoing craniotomy. During carotid endarterectomy, SUFENTA-nitrous oxide/oxygen produced reductions in cerebral blood flow comparable to those of enflurane-nitrous oxide/oxygen. During cardiovascular surgery, SUFENTA-oxygen produced EEG patterns similar to fentanyl-oxygen; these EEG changes were judged to be compatible with adequate general anesthesia.

The intraoperative use of SUFENTA at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. The incidence of postoperative hypertension, need for vasoactive agents and requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of SUFENTA as compared to patients given inhalation agents.

Skeletal muscle rigidity is related to the dose and speed of administration of SUFENTA. This muscular rigidity may occur unless preventative measures are taken (see Warnings).

Decreased respiratory drive and increased airway resistance occur with SUFENTA. The duration and degree of respiratory depression are dose related when SUFENTA is used at sub-anesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced.

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate)is indicated:

as an analgesic adjunct in the maintenance of balanced general anesthesia.

as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg).

The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.

Vital signs should be monitored routinely.

Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY).

The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent.

High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area.

Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced

Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compro-mised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits.

There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%) hypertension (3%), chest wall rigidity (3%) and bradycardia (3%).

Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

See dosage range chart for the use of SUFENTA by intravenous injection 1) in doses of up to 8 µg/kg as an analgesic adjunct to general anesthesia, and 2) in doses ≥8 µg/kg as a primary anesthetic agent for induction and maintenance of anesthesia with 100% oxygen.

Usage in Children: For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 µg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of up to 25-50 µg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.

Premedication: The selection of preanesthetic medications should be based upon the needs of the individual patient.

Neuromuscular Blocking Agents: The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

ADULT DOSAGE RANGE CHART

TOTAL DOSAGE	**MAINTENANCE DOSAGE**
ADMINISTRATION WITH NITROUS OXIDE/OXYGEN FOR SURGICAL PROCEDURES LASTING UP TO EIGHT HOURS: **• TOTAL DOSAGE REQUIREMENTS OF 1µG/KG/HR OR LESS ARE RECOMMENDED**	
1-2 µg/kg: Expected duration of anesthesia 1-2 hours. Approximately 75% or more of total SUFENTA dosage may be administered prior to intubation. Administered with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.	**10-25 µg (0.2-0.5 ml):** as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to remaining operative time anticipated.
2-8 µg/kg: Expected duration of anesthesia 2-8 hours. Approximately 50 to 75% of total SUFENTA dosage may be administered prior to intubation. Administered with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures. At dosages in this range, SUFENTA has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli, provide hemodynamic stability, and provide relatively rapid recovery.	**10-50 µg (0.2-1 ml):** as determined by changes in vital signs that indicate stress or lightening of analgesia. Supplemental dosages should be individualized, and adjusted to the remaining operative time anticipated.
ADMINISTRATION WITH 100% OXYGEN	
8-30 µg/kg: (anesthetic doses) administered with 100% oxygen and a muscle relaxant. SUFENTA has been found to produce sleep at dosages ≥8 µg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. At dosages in this range of up to 25 µg/kg, catecholamine release is attenuated. Dosages of 25-30 µg/kg have been shown to block sympathetic responses including catecholamine release. High doses are indicated in patients undergoing major surgical procedures, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance. Postoperative mechanical ventilation and observation are essential at these dosages due to extended postoperative respiratory depression.	**25-50 µg/kg (0.5-1 ml):** as determined by changes in vital signs that indicate stress and lightening of anesthesia.

In patients administered high (anesthetic) doses of SUFENTA, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

For purposes of administering small volumes of SUFENTA accurately, the use of a tuberculin syringe or equivalent is recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED: SUFENTA (sufentanil citrate) Injection for intravenous use is available as:

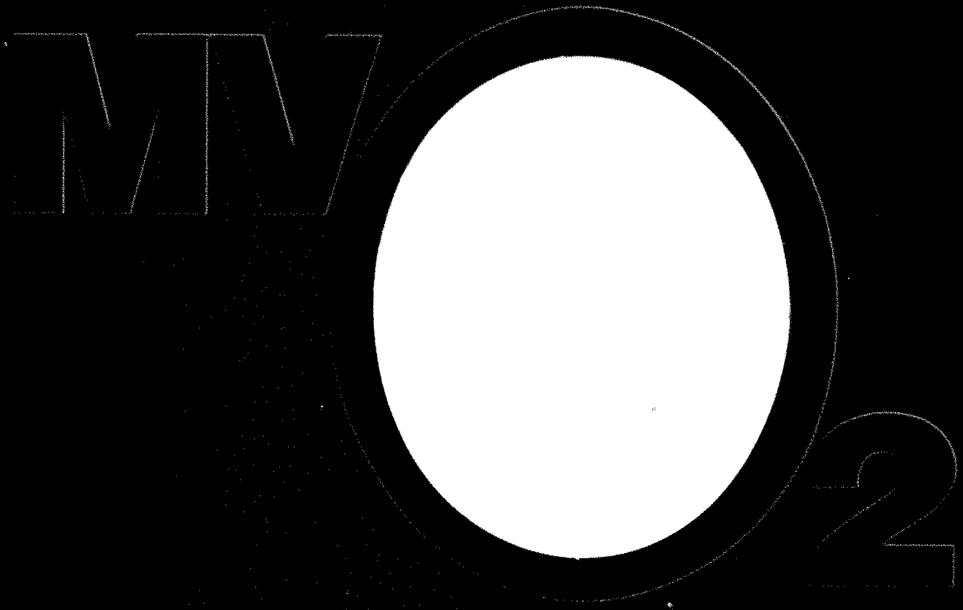
NDC 50458-050-01	50 µg/ml, 1 ml ampoules in packages of 10
NDC 50458-050-02	50 µg/ml, 2 ml ampoules in packages of 10
NDC 50458-050-05	50 µg/ml, 5 ml ampoules in packages of 10

Protect from light.
Store at room temperature.

JANSSEN
PHARMACEUTICA
Janssen Pharmaceutica Inc.
Piscataway, NJ 08854

U.S Patent No. 3,998,834
7618503-M
May 1984, January 1986

Myocardial ischemia
is often
a major concern in
heart failure...



Now...
an inotropic agent that
does not increase MVO_2

energy efficient

Inocor® I.V.

(AMRINONE)

The energy-efficient inotrope that doesn't increase myocardial oxygen demand[1]

- ○ Improves cardiac efficiency without ischemic penalty*
- ○ Substantially increases contractility
- ○ No ECG evidence of ischemic change
- ○ Can be used with benefit in patients with myocardial ischemia
- ○ INOCOR is intended for short-term use in patients who can be closely monitored and do not respond adequately to prior treatment with digitalis, diuretics, and/or vasodilators.

*For important product information concerning contraindications, adverse reactions, patient selection, and precautionary recommendations, please see last page.

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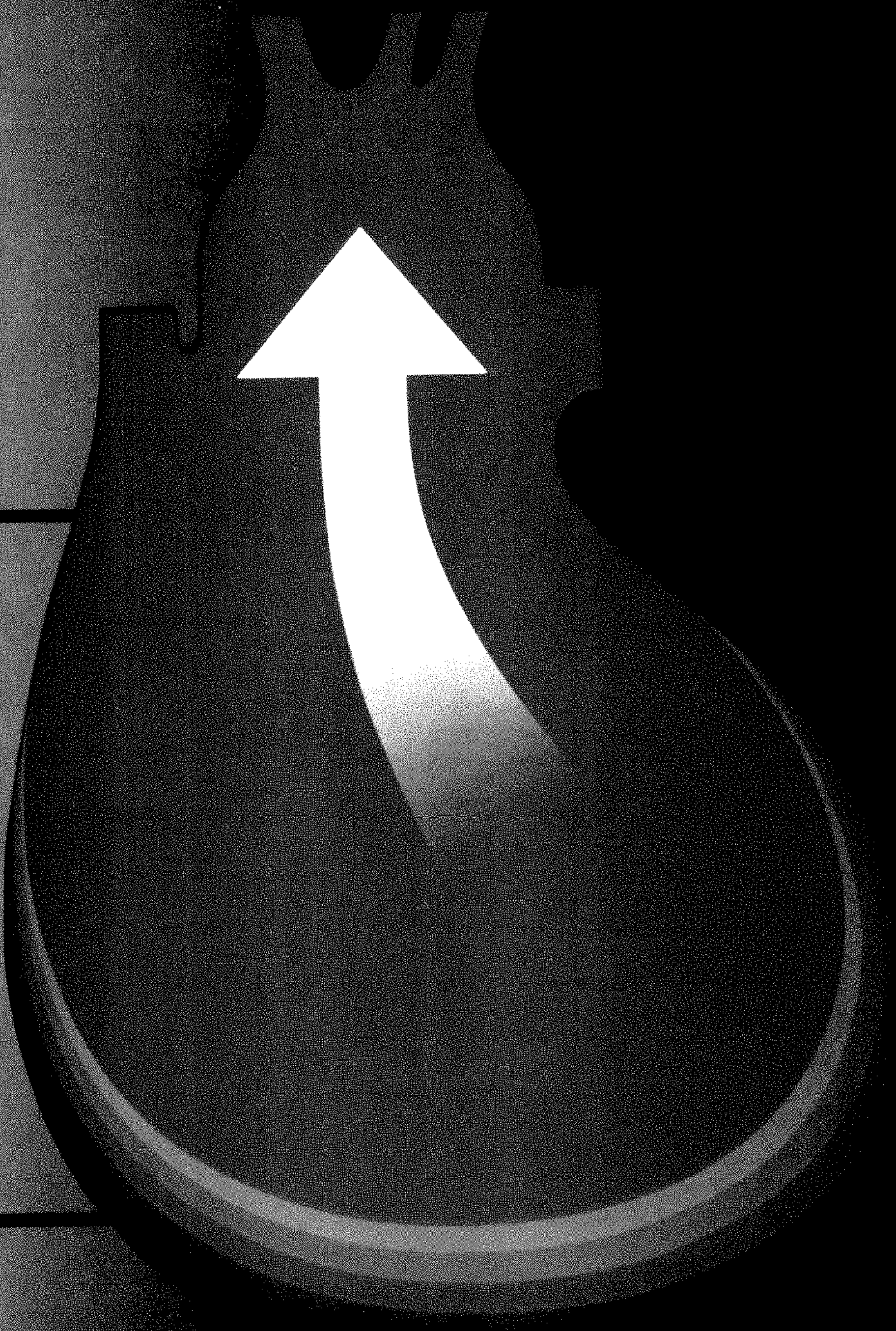


Instead of catecholamines

for the short-term management of heart failure

energy efficient

Inocor® I.V.

(AMRINONE)

A major advance toward better inotropic therapy

energy efficient

Inocor® I.V.

(AMRINONE)

Instead of catecholamines for the short-term management of heart failure

- Independent of the effects of digitalis and catecholamines
- Hemodynamics rapidly improved
- Heart rate and blood pressure not significantly changed... has not been shown to increase risk of arrhythmias (see precautions)
- Can be used in patients with myocardial ischemia
- Benefits sustained during therapy... no evidence of tachyphylaxis
- Easy to administer

Patients receiving INOCOR should be carefully monitored with the following laboratory studies: platelet counts, liver enzymes, fluid and electrolyte changes, and renal function. Hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

1. Benotti JR, Grossman W, Braunwald E, et al: Effects of amrinone on myocardial energy metabolism and hemodynamics in patients with severe congestive heart failure due to coronary artery disease. *Circulation* 1980;62:28-34.

Please see brief summary of product information on this page for contraindications, adverse reactions, patient selection, and precautionary recommendations.

Winthrop-Breon

Winthrop-Breon Laboratories, Division of Sterling Drug Inc., New York, NY 10016

61065

INOCOR lactate injection, brand of amrinone lactate, represents a new class of cardiac inotropic agents with vasodilator activity, distinct from digitalis glycosides or catecholamines.

INDICATIONS AND USAGE (INOCOR lactate injection is indicated for the short-term management of congestive heart failure in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators.)

INOCOR lactate injection is indicated for the short-term management of congestive heart failure. Because of limited experience and potential for serious adverse effects (see ADVERSE REACTIONS), INOCOR should be used only in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators. Although most patients have been studied hemodynamically for periods only up to 24 hours, some patients were studied for longer periods and demonstrated consistent hemodynamic and clinical effects. The duration of therapy should depend on patient responsiveness.

CONTRAINDICATIONS INOCOR lactate injection is contraindicated in patients who are hypersensitive to it.

It is also contraindicated in those patients known to be hypersensitive to bisulfites.

PRECAUTIONS *General:* INOCOR lactate injection should not be used in patients with severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

During intravenous therapy with INOCOR lactate injection, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients showing excessive decreases in blood pressure.

Patients who have received vigorous diuretic therapy may have insufficient cardiac filling pressure to respond adequately to INOCOR lactate injection, in which case cautious liberalization of fluid and electrolyte intake may be indicated.

Supraventricular and ventricular arrhythmias have been observed in the very high-risk population treated. While amrinone per se has not been shown to be arrhythmogenic, the potential for arrhythmia, present in congestive heart failure itself, may be increased by any drug or combination of drugs.

Thrombocytopenia and hepatotoxicity have been noted (see ADVERSE REACTIONS).

LABORATORY TESTS *Fluid and electrolytes:* Fluid and electrolyte changes and renal function should be carefully monitored during amrinone lactate therapy. Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalized patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

DRUG INTERACTIONS In a relatively limited experience, no untoward clinical manifestations have been observed in patients in whom INOCOR lactate injection was used concurrently with the following drugs: digitalis glycosides, lidocaine, quinidine, metoprolol, propranolol; hydralazine, prazosin, isosorbide dinitrate, nitroglycerine; chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, captopril, heparin, warfarin, potassium supplements, insulin, diazepam.

One case of excessive hypotension was reported when amrinone was used concurrently with disopyramide.

Until additional experience is available, concurrent administration with Norpace® disopyramide should be undertaken with caution.

USE IN ACUTE MYOCARDIAL INFARCTION INOCOR is not recommended for use in acute myocardial infarction.

USE IN CHILDREN Safety and effectiveness in children have not been established

USE IN PREGNANCY *Pregnancy category C:* In New Zealand white rabbits, amrinone has been shown to reduce fetal skeletal and gross external malformations at oral doses of 16 mg/kg and 50 mg/kg that were toxic for the rabbit. Studies in French Hy/Cr rabbits using oral doses up to 32 mg/kg/day did not confirm this finding. No malformations were seen in rats receiving amrinone intravenously at the maximum dose used, 15 mg/kg/day (approximately the recommended daily IV dose for patients with congestive heart failure). There are no adequate and well-controlled studies in pregnant women. Amrinone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

USE IN NURSING MOTHERS Caution should be exercised when amrinone is administered to nursing women, since it is not known whether it is excreted in human milk.

ADVERSE REACTIONS *Thrombocytopenia:* Intravenous INOCOR lactate injection resulted in platelet count reductions to below 100,000/mm³ in 2.4% of patients.

Gastrointestinal effects: Gastrointestinal adverse reactions reported with INOCOR lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdominal pain (0.4%), and anorexia (0.4%).

Cardiovascular effects: Cardiovascular adverse reactions reported with INOCOR lactate injection include arrhythmia (3%) and hypotension (1.3%).

Hepatic toxicity: In dogs, at IV doses between 9 mg/kg/day and 32 mg/kg/day, amrinone showed dose-related hepatotoxicity manifested either as enzyme elevation or hepatic cell necrosis or both. Hepatotoxicity has been observed in man following long-term oral dosing and has been observed, in a limited experience (0.2%), following IV administration of amrinone.

Hypersensitivity: There have been reports of several apparent hypersensitivity reactions in patients treated with oral amrinone for about two weeks. Signs and symptoms were variable but included pericarditis, pleuritis, and ascites (one case); myositis with interstitial shadowing on chest x-ray and elevated sedimentation rate (one case); and vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (one case). The first patient died, not necessarily of the possible reaction, while the last two resolved with discontinuation of therapy. None of the cases were rechallenged, so attribution to amrinone is not certain, but possible hypersensitivity reactions should be considered in any patient maintained for a prolonged period on amrinone

General: Additional adverse reactions observed in intravenous amrinone clinical studies include fever (0.9%), chest pain (0.2%), and burning at the site of injection (0.2%).

OVERDOSAGE Doses of INOCOR lactate injection may produce hypotension because of its vasodilator effect. If this occurs, amrinone administration should be reduced or discontinued. No specific antidote is known, but general measures for circulatory support should be taken

MANAGEMENT OF ADVERSE REACTIONS *Platelet count reductions:* Asymptomatic platelet count reduction (to less than 150,000/mm³) may be reversed within one week of a decrease in drug dosage. Further, with no change in drug dosage, the count may stabilize at lower than predrug levels without any clinical sequelae. Predrug platelet counts and frequent platelet counts during therapy are recommended to assist in decisions regarding dosage modifications

Should a platelet count less than 150,000/mm³ occur, the following actions may be considered:

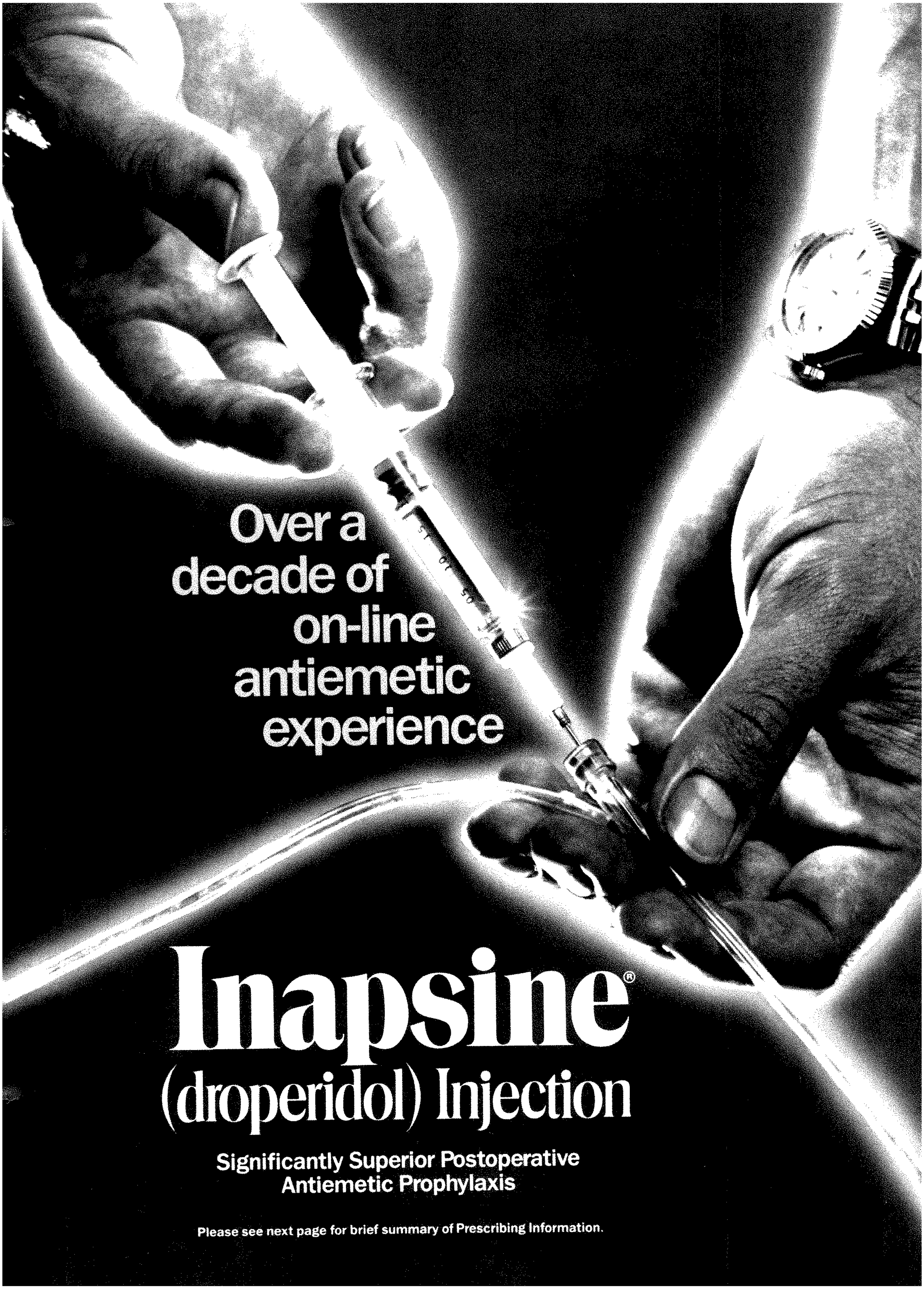
- Maintain total daily dose unchanged, since in some cases counts have either stabilized or returned to pretreatment levels
- Decrease total daily dose.
- Discontinue amrinone if, in the clinical judgment of the physician, risk exceeds the potential benefit.

Gastrointestinal side effects: While gastrointestinal side effects were seen infrequently with IV therapy, should severe or debilitating ones occur, the physician may wish to reduce dosage or discontinue the drug based on the usual benefit-to-risk considerations.

Hepatic toxicity: In clinical experience to date with IV administration, hepatotoxicity has rarely been observed. If acute marked alterations in liver enzymes occur together with clinical symptoms, suggesting an idiosyncratic hypersensitivity reaction, amrinone therapy should be promptly discontinued

If less than marked enzyme alterations occur without clinical symptoms, these nonspecific changes should be evaluated on an individual basis. The clinician may wish to continue amrinone and reduce the dosage or discontinue the drug based on the usual benefit-to-risk considerations

HOW SUPPLIED Ampuls of 20 mL sterile, clear yellow solution containing INOCOR 5 mg/mL, box of 5 (NDC 0024-0888-20). Each 1 mL contains INOCOR lactate equivalent to 5 mg base and 0.25 mg sodium metabisulfite in water for injection



Over a
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Please see next page for brief summary of Prescribing Information.

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- Proven in double-blind studies to provide postoperative antiemetic effect (when given perioperatively) that is significantly superior to placebo,[1,2] diazepam[2] and hydroxyzine[2,3]
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- May be administered *intraoperatively* in long procedures as well as preoperatively in both long and short procedures
- Helps maintain cardiovascular stability by protecting against hypertensive episodes, heart rate changes and the pressor and arrhythmogenic effects of epinephrine
- Facilitates a comfortable, anxiety-free emergence, reducing the need for postoperative opioids

Inapsine®
(droperidol) Injection

Significantly Superior Postoperative Antiemetic Prophylaxis

Before prescribing please consult complete prescribing information, of which the following is a brief summary.
Protect from light. Store at room temperature.
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY.
Droperidol is a neuroleptic (tranquilizer) agent.

DESCRIPTION: *2 ml. and 5 ml. ampoules:* Each ml. contains Droperidol 2.5 mg. and lactic acid for pH adjustment to 3.4 ± 0.4
10 ml. vials: Each ml. contains Droperidol 2.5 mg. with 1.8 mg. methylparaben and 0.2 mg. propylparaben, and lactic acid for pH adjustment to 3.4 ± 0.4

INDICATIONS: INAPSINE (droperidol) is indicated: • to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures; • for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia; • in neuroleptanalgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE* (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE.
As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.

If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.

PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms, INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.

Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effect with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias. (See full prescribing information for complete description.)

ADVERSE REACTIONS: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).

When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur; if these remain untreated, respiratory arrest could occur.

Elevated blood pressure, with or without pre-existing hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

Usual Adult Dosage

I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.

II. Adjunct to General Anesthesia
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

If INNOVAR* injection is administered in addition to INAPSINE (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Insert for full prescribing information.

III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml.) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.

IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

How Supplied: *2 ml. and 5 ml. ampoules*—packages of 10;
10 ml. multiple-dose vials—packages of 10.
U.S. Patent No. 3,161,645
NDC 50458-010-02; NDC 50458-010-05, NDC 50458-010-10
March 1980, Revised June 1980 IP41C98-M

Manufactured by TAYLOR PHARMACAL CO. for

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PHARMACEUTICA

Janssen Pharmaceutica Inc., Piscataway, New Jersey 08854

REFERENCES: 1. Patton CM Jr, Moon MR, Dannemiller FJ: The prophylactic antiemetic effect of droperidol. *Anesth Anal* 1974;53:361-364
2. Tornetta FJ: A comparison of droperidol, diazepam, and hydroxyzine hydrochloride as premedication. *Anesth Anal* 1977;56:496-500.
3. Mehta P, Theriot E, Mehrotra D, et al: Comparative evaluation of preanesthetic medications. *Curr Ther Res* 1984;35:715-720

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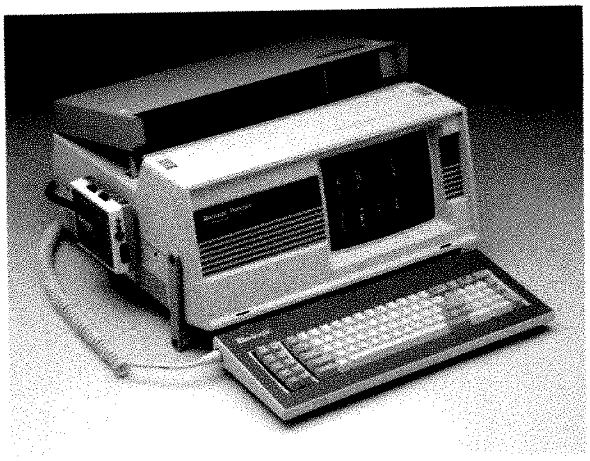
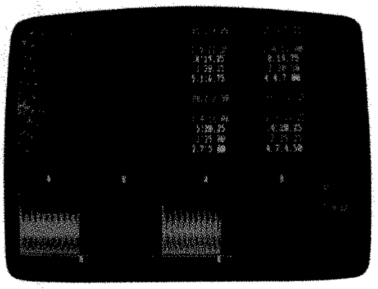
Generations ahead in analyzing EEG



The New Bio-logic® Compressed Spectral Array

You can now have advanced CSA capability neatly packaged in a single carrying case ready to take with you to the operating room, recovery room or intensive care unit. The NEW Compressed Spectral Array, now available on all Bio-logic systems, is especially impressive when presented on the portable Traveler. This new IBM PC compatible system is so easy to use that extensive training won't be necessary. Your keyboard controlled high-tech assistant will guide you with onscreen prompts.*



Two channels of EEG activity, with waves, time plots, and numerical analyses.

The CSA Solution

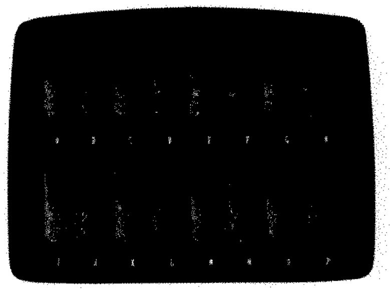
Determining patients' condition from the appearance of their EEG demands considerable scrutiny. Yet this information is crucial in many situations commonly faced by the physician. Depth of anesthesia, for example, is clearly indexed by EEG. But because of drawbacks stemming from difficulty of data gathering and interpretation, it often is not used for this purpose. The Bio-logic CSA provides a means of abstracting the essence of the EEG message and displaying it in a convenient and easy-to-comprehend form.

Flexible Advanced Capability

You can save pounds of paper because the EEG can be reduced to user selected blocks of time which can be viewed instantaneously on the video screen. Also, you may choose to print out those selected blocks of time or store the data for subsequent evaluation. You can recognize the frequency shifts and amplitude changes in six bands of the power spectrum at a glance. Processed EEG may be displayed on any combination of three display formats: trend analysis, numeric plot, and CSA graphics. A built-in impedance test allows you to quickly check electrode impedance at any time. The optional color display enhances the differentiation between channels.

Expandability

The CSA Traveler provides up to four channels of capability with single or dual floppy disk storage. Maintaining the standards set by the powerful Bio-logic System 7, Navigator and Brain Atlas, which offer up to 19 channels of CSA capability, the Traveler is truly expandable. You can add auditory, visual and somatosensory evoked potential testing, as well as ENG, ENN, NCV, Bone Conduction, ECoG, 40 Hz ERP, and still have a portable system. Actually, with additional hardware components, the CSA Traveler can even be expanded to include ERG, EOG and topographic brain mapping.



Sixteen channels of CSA activity using waveform display mode.

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Just like the other revolutionary Bio-logic systems, the CSA Traveler is remarkably affordable. Incorporating state-of-the-art technology, Bio-logic continues to challenge the industry by offering the ultimate in capability for a reasonable price.

Customer Support

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Undetected hypoxia is known to be the most common cause of anesthetic related mortality. Unfortunately, the standardly monitored variables of heart rate, blood pressure and skin color are not sensitive enough to give an early warning of hypoxia. Practitioners need an edge–an early warning of hypoxia–to fight back.

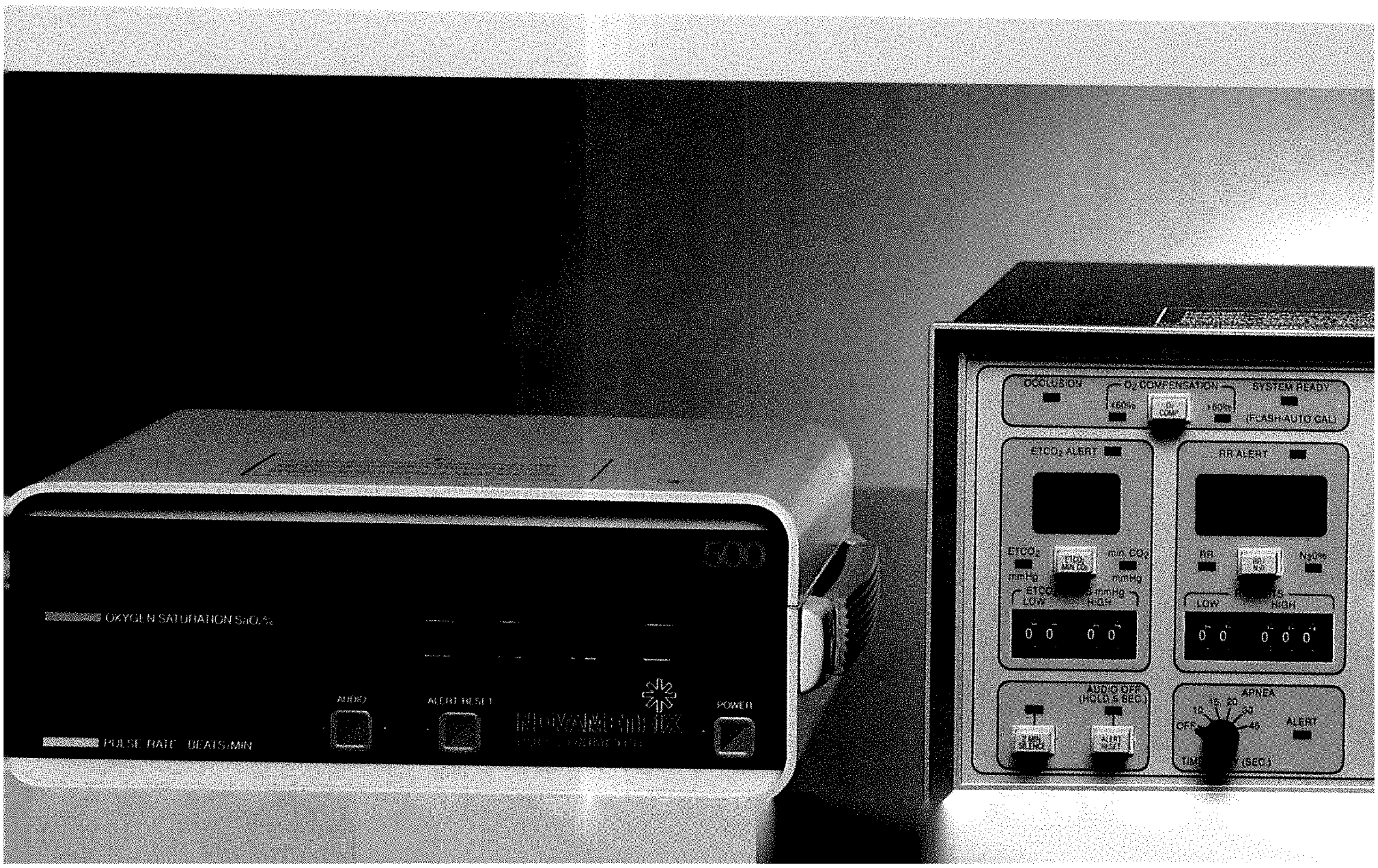
Fortunately, the concerned practitioner can now select a variety of non-invasive techniques for O_2/CO_2 monitoring which are both practical and affordable. Choosing which technique can be complicated. And which manufacturer even more so. Or, you can choose Novametrix.

Novametrix is the only company that manufactures all three types of continuous O_2/CO_2 monitoring systems. We recognize that all three have important roles in clinical practice. We keep the complications to a minimum. And we leave the choice up to you.

Novametrix has been out front among system manufacturers for nearly a decade. We pioneered the transcutaneous O_2/CO_2 CO_2 MMO_2 N SENSOR™ electrode, and more innovations that have become industry standards. Our monitors are more reliable, easier to use and read, simpler to maintain than others. Because you can't afford complications.

No complications, either, in Novametrix' sales support and service. We stand behind every system we sell. Our sales reps understand your needs as well as our product lines. They can help you make the right choice. And we'll give you all the training you need to get the most from the systems you choose.

Protect your patients–and yourself. No complications. Choose one or more O_2/CO_2 monitoring systems from Novametrix. Call us toll-free at **1-800-243-3444.** Or write Novametrix Medical Systems Inc., 1 Barnes Industrial Park Road, P.O. Box 690, Wallingford, CT 06492.



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When pulse oximetry–measuring the percentage O_2 saturation of arterial blood–is the technology of choice, the choice is Novametrix. Accurate and reliable, the Model 500 Pulse Oximeter requires no warm-up time and sets up fast with its own self-diagnostic check. The simple, easy to use message center programs high and low alert limits, which are retained in memory. Large, easy to read displays are enhanced with a separate pulse amplitude bar graph. Small and lightweight, this microprocessor based system can run up to 20 hours on a single battery recharge. The leader in sensor technology, Novametrix provides a variety of trouble-free, reusable sensors for every application.

End Tidal CO_2

Finally, an End Tidal $CO/_2$ monitor which needs no calibration. Exclusive auto-zeroing gives you total accuracy. The calibration needs to be checked only once every six months because medical professionals demand simplicity and reliability.

Condensation problems plague end tidal monitors. But not Novametrix. Our exclusive dehumidification interface kit eliminates troublesome water traps. Sophisticated electronics. Simple operation. Features like large LED readouts, one-button alarm, and apnea alert. Our system meets the toughest professional demands.

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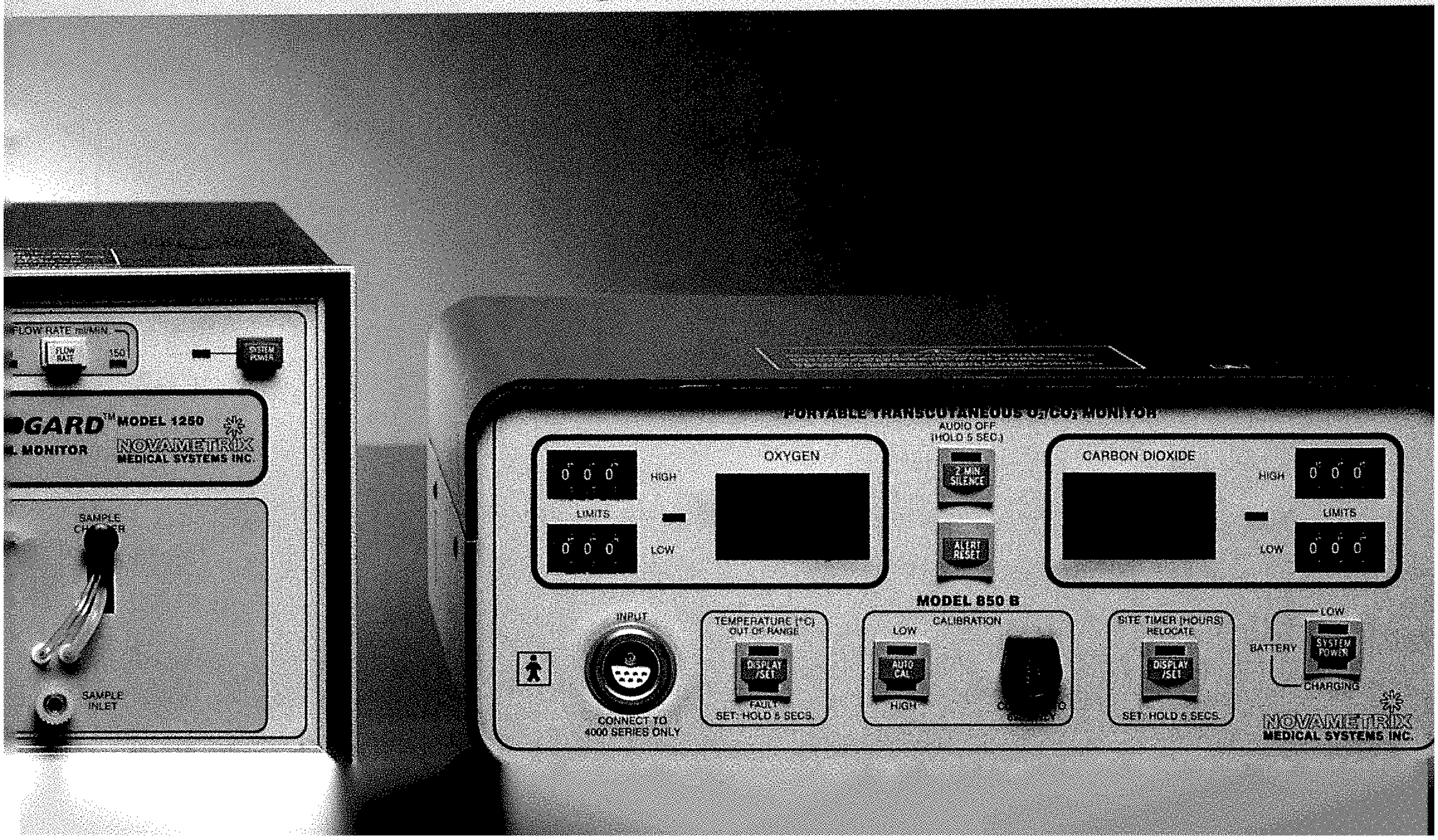
Novametrix continues to lead the industry in transcutaneous monitoring systems. In the OR, at the bedside, and in transport, there's no easier way to effectively and continuously monitor skin tissue O_2 and CO_2.

One sensor is all it takes. Just switch on the power, push the auto-cal button, and you're ready to monitor. Run on AC power or on a rechargeable battery for up to 8 hours.

A no-nonsense front panel features simple pushbutton controls and alert limits, and easy-to-read displays. Operation is smooth and trouble-free. Sensor reponse is quick, with minimal drift. Everything you want in a transcutaneous monitoring system. That's why Novametrix has sold more than anyone else.

NOVAMETRIX



Albumin & PPF are no safer or more effective than Hespan®

(hetastarch)

...they're simply

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As safe as albumin or PPF

In comparative clinical studies, platelet counts, hematocrits, serum fibrinogen levels, prothrombin times (PT), and partial thromboplastin times (PTT) seen with Hespan were comparable to those seen with albumin or plasma protein fraction (PPF).[1,2]

Other studies demonstrate that when any reduction in platelet count or prolongation of PT or PTT does occur with Hespan, no increased bleeding results, even in patients with multiple trauma.[3-5] As with any volume expander, patients should be monitored for excessive hemodilution of coagulant factors or circulatory overload when large volumes are administered.

When Hespan-treated patients were monitored to detect localized or systemic sepsis, there was no evidence of a decrease in their ability to ward off infection or combat an established infection.[5]

Hespan is nonantigenic and, as with blood-derived colloids, any risk of allergic reaction is minimal. Hespan also has a negligible effect on subsequent blood typing or crossmatching.[6]

As effective as albumin or PPF

Comparative clinical studies have repeatedly demonstrated that Hespan is as effective as albumin or PPF in postoperative myocardial revascularization,[1-3] and hemorrhagic, traumatic, or septic shock.[4,5,7]

No significant differences between Hespan and albumin or PPF were noted in any efficacy parameter.[1-5,7] Hespan effectively maintained colloid osmotic pressure, restored plasma volume, and improved cardiac output and renal function in hypovolemic patients.[1-5,7] And, the volume-expanding effect of a single infusion of Hespan can persist for 24 hours or longer.

Half the price of albumin or PPF

Hespan offers a potential savings to your hospital of tens of thousands of dollars a year.

double the price.

For additional information, contact the Medical Services Department, American Critical Care, 1600 Waukegan Road, McGaw Park, IL 60085. Phone 1-800-323-4980.

Lifesaving, moneysaving

HESPAN®
(hetastarch)

American Critical Care

American Hospital Supply Corporation

Please see references and brief summary of prescribing information on following page.

References: 1. Diehl JT, Lester JL, Cosgrove DM: Clinical comparison of hetastarch and albumin in postoperative cardiac patients. *Ann Thorac Surg 34* (6):674-679, 1982. 2. Moggio RA, Rha CC, Somberg ED, et al: Hemodynamic comparison of albumin and hydroxyethyl starch in postoperative cardiac surgery patients. *Crit Care Med 11* (12):943-945, 1983. 3. Kirklin JK, Lell WA, Kouchoukos NT: Hydroxyethyl starch versus albumin for colloid infusion following cardiopulmonary bypass in patients undergoing myocardial revascularization. *Ann Thorac Surg 37* (1):40-46, 1984. 4. Puri VK, Paidipaty B, White L: Hydroxyethyl starch for resuscitation of patients with hypovolemia and shock. *Crit Care Med 9* (12):833-837, 1981. 5. Shatney CH, Deepika K, Militello PR, et al: Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. *Arch Surg 118*:804-809, 1983. 6. Daniels MJ, Strauss RG, Smith-Floss AM: Effects of hydroxyethyl starch on erythrocyte typing and blood crossmatching. *Transfusion 22* (3):226-228, 1982. 7. Rackow EC, Falk JL, Fein IA, et al: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med 11*(11):839-850, 1983.

HESPAN® (hetastarch)

6% Hetastarch in 0.9% Sodium Chloride Injection

CONTRAINDICATIONS

Hetastarch is contraindicated in patients with severe bleeding disorders or with severe congestive cardiac and renal failure with oliguria or anuria.

WARNINGS

Large volumes may alter the coagulation mechanism. Thus, administration of hetastarch may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of hetastarch.

Usage in Leukapheresis: Significant declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures due to the volume expanding effects of hetastarch. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by hetastarch and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values.

Usage in Pregnancy: Reproduction studies have been done in mice with no evidence of fetal damage. Relevance to humans is not known since hetastarch has not been given to pregnant women. Therefore, it should not be used in pregnant women, particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the potential hazards.

Usage in Children: No data available pertaining to use in children.

The safety and compatibility of additives have not been established.

PRECAUTIONS

The possibility of circulatory overload should be kept in mind. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Indirect bilirubin levels of 0.83 mg% (normal 0.0-0.7 mg%) have been reported in 2 out of 20 normal subjects who received multiple hetastarch infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering hetastarch to patients with a history of liver disease.

Regular and frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of hetastarch use during leukapheresis. Studies should include CBC, total leukocyte and platelet counts, leukocyte differential count, hemoglobin, hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT).

Hetastarch is nonantigenic. However, allergic or sensitivity reactions have been reported (see ADVERSE REACTIONS). If such reactions occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

ADVERSE REACTIONS

The following have been reported: vomiting, mild temperature elevation, chills, itching, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, and anaphylactoid reactions consisting of periorbital edema, urticaria, and wheezing.

HOW SUPPLIED

NDC 0094-0037-05-Hespan® (6% Hetastarch in 0.9% Sodium Chloride Injection) is supplied sterile and nonpyrogenic in 500 ml intravenous infusion bottles.

CAUTION

Federal (U.S.A.) law prohibits dispensing without prescription.

Rev: Feb., 1982

Distributed by

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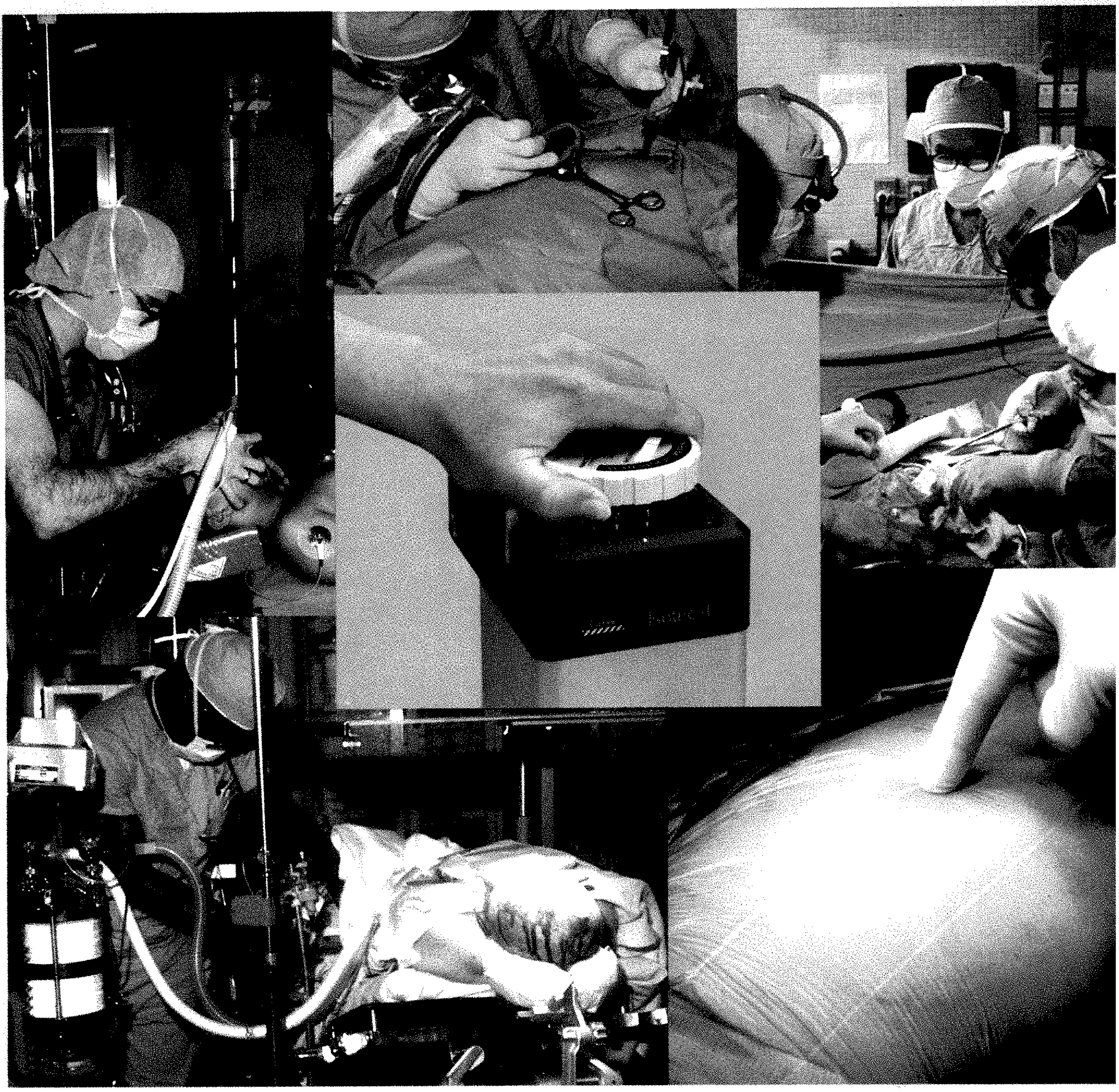

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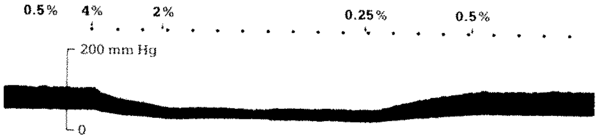
A hypotensive agent for craniotomy and clipping of aneurysms

Isoflurane may be used as both anesthetic and hypotensive agent, providing for precise control of blood pressure throughout procedures such as clipping of cerebral aneurysms.[1]



Blood pressure tracing demonstrating the rapid response of systemic blood pressure to changes in inspired isoflurane concentration. The arrows indicate the changes in isoflurane concentration and the dots mark 1-min intervals. Mean blood pressure during the normotensive period was 70 mm Hg and 40 mm Hg during the hypotensive phase.[1]

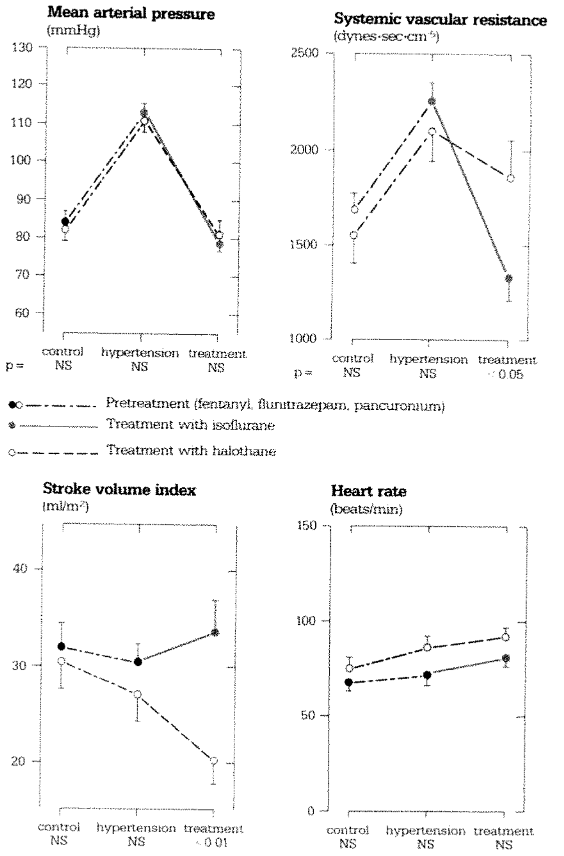
Control of intracranial pressure for craniotomy and excision of space-occupying lesion

Isoflurane causes no increase in intracranial pressure (ICP) when $PaCO_2$ is controlled at 25-30 torr, and ICP may be readily lowered *during surgery* by decreasing $PaCO_2$.[2]

Control of hypertension during coronary artery bypass surgery

Control of intraoperative hypertension may be achieved with isoflurane by lowering peripheral vascular resistance (left ventricular afterload) generally without depressing stroke volume or increasing heart rate. These effects can be of particular benefit in patients with compromised left ventricular function. Halothane is equally effective in lowering blood pressure without increasing heart rate, but it decreases stroke volume.

Treatment of hypertension with either isoflurane or halothane anesthesia in patients undergoing coronary artery bypass surgery (Adapted from Hess et al[3]).



Potentiation of relaxants for orthopedic surgery

With isoflurane anesthesia, profound surgical muscle relaxation can be provided with one-third to two-thirds the usual relaxant dose (pancuronium, d-tubocurarine or atracurium).[4,5] Thus the recovery period may be shortened and the need for reversal agents reduced by the rapid elimination of isoflurane.

Stability of heart rhythm when full hemostatic doses of epinephrine are needed

"Isoflurane, like enflurane, produces stable cardiac rhythm and, unlike halothane, does not sensitize the myocardium to the effects of catecholamines."[6]

A rapid recovery with few post-anesthetic symptoms for outpatient surgery

"Isoflurane is eliminated more rapidly than any other potent modern inhaled anesthetic."[7] (Blood-gas partition coefficient, only 1.4)

Anesthesia using isoflurane in a mixture of oxygen and air produced a significantly lower incidence of nausea and vomiting following outpatient laparoscopy than anesthesia that included nitrous oxide.[8]

Post-laparoscopy Nausea (N) and Vomiting (V)

Group	No. of Patients	No. of Patients with N or N&V
fentanyl, N_2O, O_2	37	23 (62%)*
isoflurane, fentanyl, O_2	20	6 (30%)
isoflurane, O_2	20	5 (25%)

Adapted from Alexander et al[8] *$p<0.05$

References:

1. Lam AM, Gelb AW: Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. Anesth Analg 62:742-748, 1983.
2. Adams RW et al: Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. Anesthesiology 54:97-99, 1981.
3. Hess W et al: Comparison of isoflurane and halothane when used to control intraoperative hypertension in patients undergoing coronary artery bypass surgery. Anesth Analg 62:15-20, 1983.
4. Miller RD et al: Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. Anesthesiology 35:509-514, 1971.
5. Tracrium® (atracurium besylate) prescribing information, Burroughs Wellcome Co., Research Triangle Park, NC 27709.
6. Wade JG, Stevens WC: Isoflurane: an anesthetic for the eighties? Anesth Analg 60(9):666-682, 1981.
7. Eger EI II: Isoflurane, a compendium and reference, Ohio Medical Anesthetics, Madison, WI, 1981.
8. Alexander GD et al: The role of nitrous oxide in postoperative nausea and vomiting. Anesth Analg 63:175, 1984.

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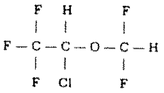
Forane®...a product of original Anaquest research

(isoflurane)

Forane®...The Versatile Anesthetic
(isoflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription

DESCRIPTION: FORANE (isoflurane) is a nonflammable general inhalation anesthetic agent It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



$$\begin{array}{ccccccccc} & & F & & H & & & & F \\ & & | & & | & & & & | \\ F & - & C & - & C & - & O & - & C - H \\ & & | & & | & & & & | \\ & & F & & Cl & & & & F \end{array}$$

Some physical constants are:

Molecular weight		184.5
Boiling point at 760 mm Hg		48.5 °C (uncorr.)
Refractive index n_D^{20}		1.2990-1.3005
Specific gravity 25 °/25 °C		1.496
Vapor pressure in mm Hg**	20 °C	238
	25 °C	295
	30 °C	367
	35 °C	450

**Equation for vapor pressure calculation:

$\log_{10}P_{vap} = A + \frac{B}{T}$ where:
$A = 8.056$
$B = -1664.58$
$T = °C + 273.16$ (Kelvin)

Partition coefficients at 37 °C	
Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.8
Partition coefficients at 25 °C - rubber and plastic	
Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5
Purity by gas chromatography	>99.9%
Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23 °C	None
Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec. and 23 °C	Greater than useful concentration in anesthesia.

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY: FORANE (isoflurane) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N_2O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal $PaCO_2$, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE: FORANE (isoflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS: Known sensitivity to FORANE (isoflurane) or to other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS: Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS: General: As with any potent general anesthetic, FORANE (isoflurane) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N_2O. See CLINICAL PHARMACOLOGY.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS: Adverse reactions encountered in the administration of FORANE (isoflurane) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period.

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE: In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSAGE AND ADMINISTRATION: Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane;
b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\%\ \text{isoflurane} = \frac{100\ P_V\ F_V}{F_T\ (P_A - P_V)}$$

where: P_A = Pressure of atmosphere
P_V = Vapor pressure of isoflurane
F_V = Flow of gas through vaporizer (mL/min)
F_T = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED: FORANE (isoflurane), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

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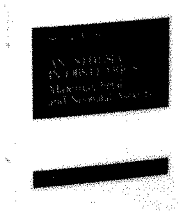
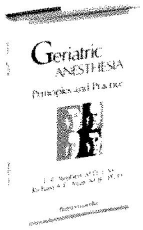

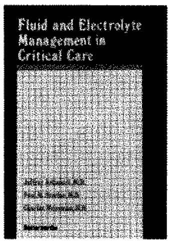

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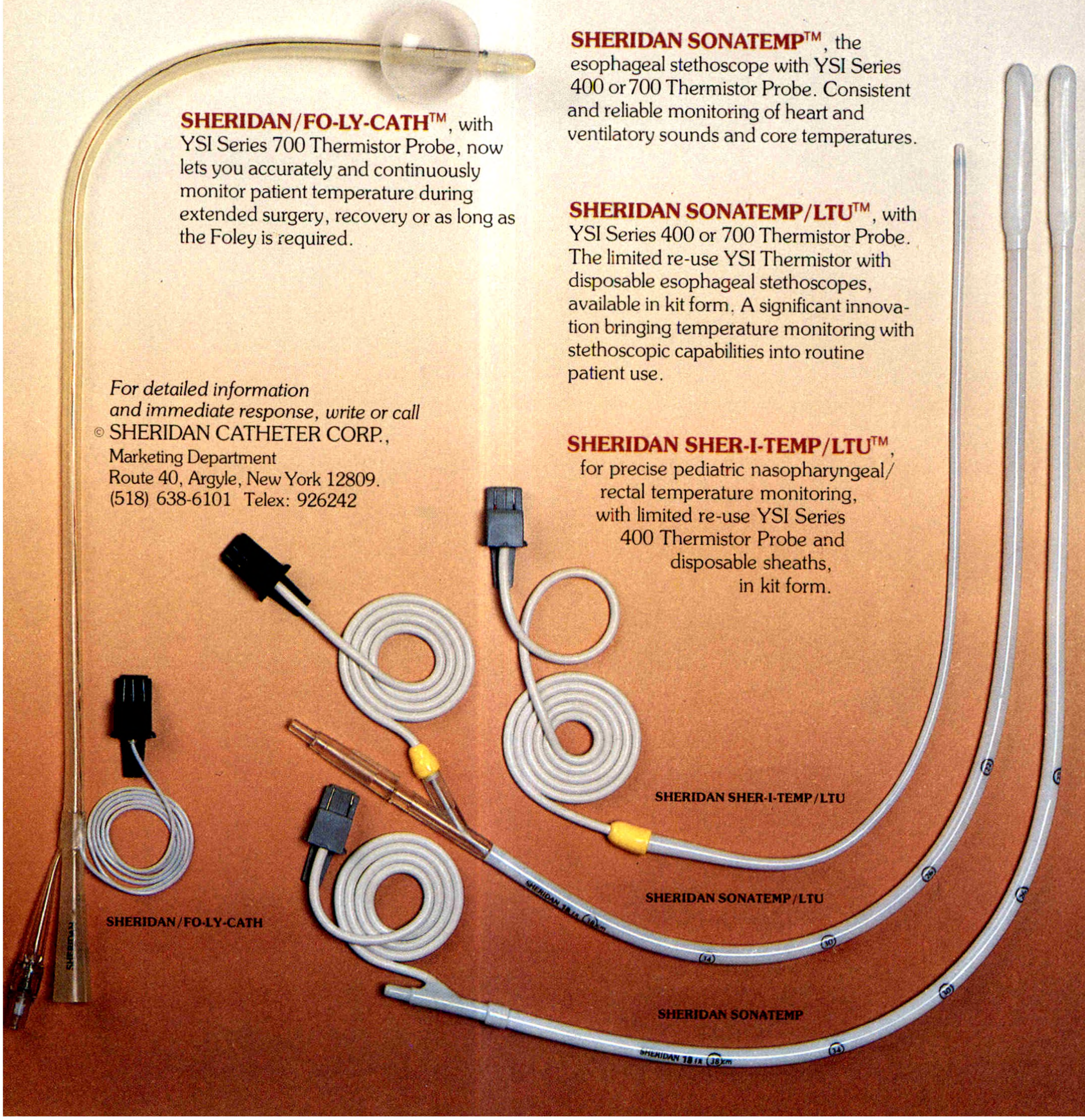

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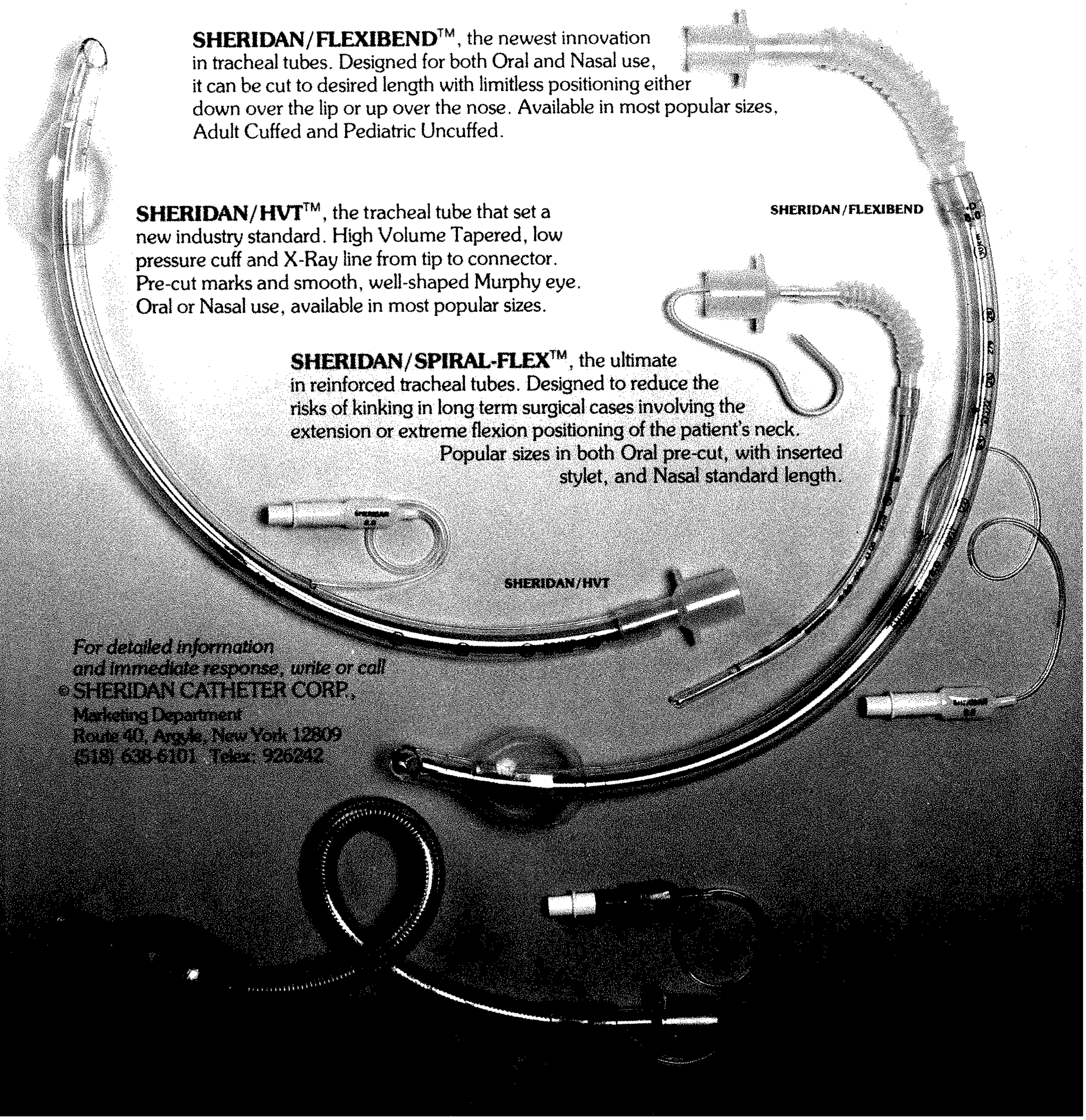

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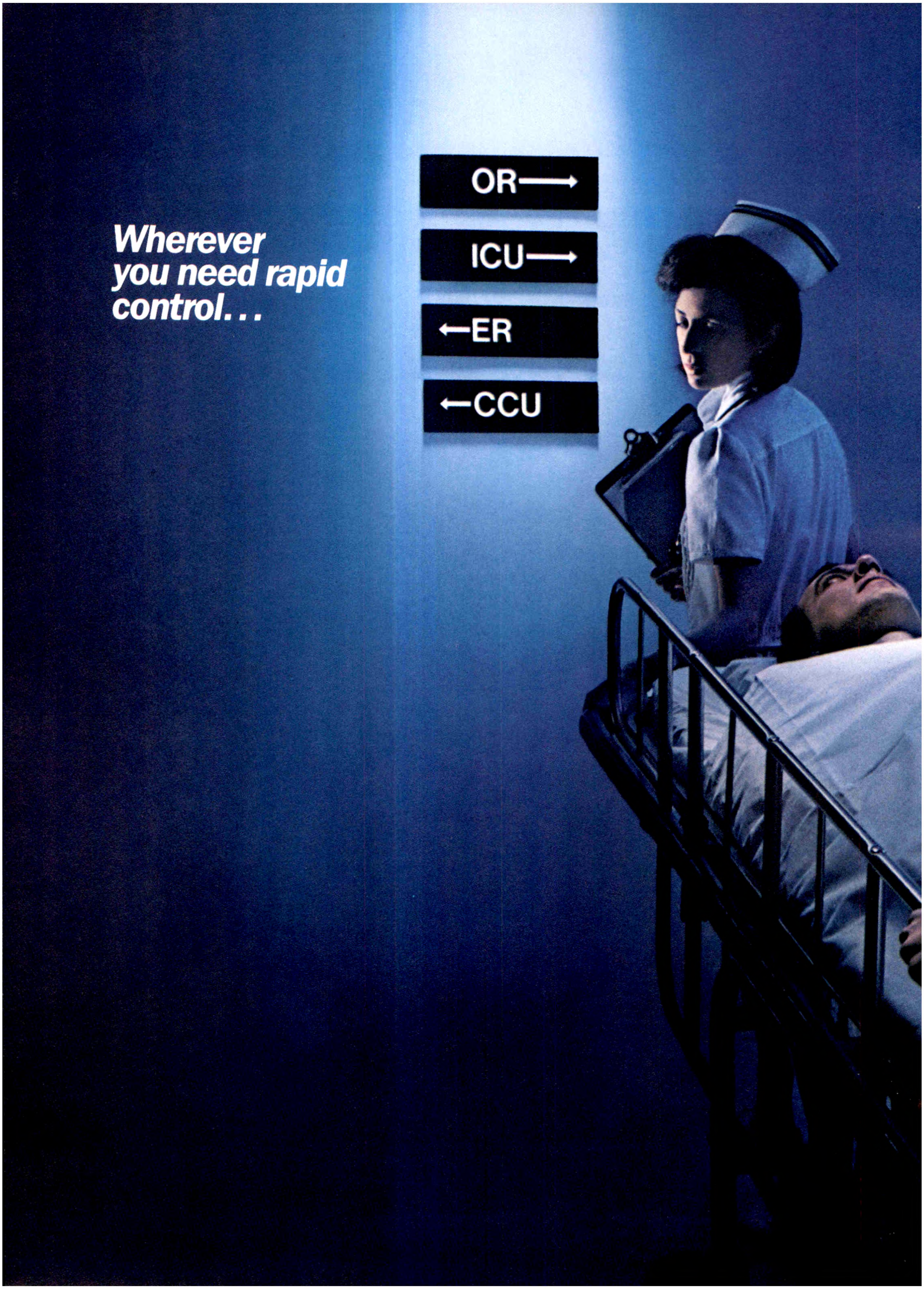
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TRANDATE Injection has no significant effect on myocardial function.[*]

☐ **Well tolerated**

The most common adverse reactions include postural hypotension,[†] dizziness,[†] paresthesias, increased sweating and nausea. See **ADVERSE REACTIONS** section of Prescribing Information before administering.

☐ **An original product of Glaxo research**

[*] TRANDATE Injection is contraindicated in bronchial asthma, overt cardiac failure, greater-than-first-degree heart block, cardiogenic shock and severe bradycardia.

[†] The episodes of postural hypotension and dizziness occurred primarily in one study in which patients were placed in an upright position within three hours of dosing for evaluation.

Patients should be kept in the supine position during IV drug administration. See **DOSAGE AND ADMINISTRATION** section of Prescribing Information before initiating therapy.

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See next page for a Brief Summary of Prescribing Information.

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TRN200

March 1986

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labetalol HCl/Glaxo 20 ml, 5 mg/ml

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INDICATIONS AND USAGE: TRANDATE® (labetalol HCl) Injection is indicated for control of blood pressure in severe hypertension.
CONTRAINDICATIONS: TRANDATE® Injection is contraindicated in bronchial asthma, overt cardiac failure, greater than first degree heart block, cardiogenic shock, and severe bradycardia (see **WARNINGS**).
WARNINGS: Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure. Beta blockade carries a potential hazard of further depressing myocardial contractility and precipitating more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, labetalol HCl can be used with caution in patients with a history of heart failure who are well-compensated. Congestive heart failure has been observed in patients receiving labetalol HCl. Labetalol HCl does not abolish the inotropic action of digitalis on heart muscle.
In Patients Without a History of Cardiac Failure: In patients with latent cardiac insufficiency, continued depression of the myocardium with beta-blocking agents over a period of time can in some cases lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, TRANDATE® therapy should be withdrawn (gradually, if possible).
Ischemic Heart Disease: Angina pectoris has not been reported upon labetalol HCl discontinuation. However, following abrupt cessation of therapy with some beta-blocking agents in patients with coronary artery disease, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Therefore, such patients should be cautioned against interruption of therapy without the physician's advice. Even in the absence of overt angina pectoris, when discontinuation of TRANDATE is planned, the patient should be carefully observed and should be advised to limit physical activity. If angina markedly worsens or acute coronary insufficiency develops, TRANDATE administration should be reinstituted promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken.
Nonallergic Bronchospasm (eg, chronic bronchitis and emphysema): Since TRANDATE Injection at the usual intravenous therapeutic doses has not been studied in patients with nonallergic bronchospastic disease, it should not be used in such patients.
Pheochromocytoma: Intravenous labetalol HCl has been shown to be effective in lowering the blood pressure and relieving symptoms in patients with pheochromocytoma; higher than usual doses may be required. However, paradoxical hypertensive responses have been reported in a few patients with this tumor; therefore, use caution when administering labetalol HCl to patients with pheochromocytoma.
Diabetes Mellitus and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (eg, tachycardia) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces the release of insulin in response to hyperglycemia; it may therefore be necessary to adjust the dose of antidiabetic drugs.
Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial. Protracted severe hypotension and difficulty in restarting or maintaining a heartbeat have been reported with beta-blockers. The effect of labetalol HCl's alpha-adrenergic activity has not been evaluated in this setting.

A synergism between labetalol HCl and halothane anesthesia has been shown (see **Drug Interactions** under **PRECAUTIONS**).
Rapid Decreases of Blood Pressure: Caution must be observed when reducing severely elevated blood pressure. Although such findings have not been reported with intravenous labetalol HCl, a number of adverse reactions, including cerebral infarction, optic nerve infarction, angina and ischemic changes in the electrocardiogram, have been reported with other agents when severely elevated blood pressure was reduced over time courses of several hours to as long as 1 or 2 days. The desired blood pressure lowering should therefore be achieved over as long a period of time as is compatible with the patient's status.
PRECAUTIONS: General: ***Impaired hepatic function*** may diminish metabolism of TRANDATE® Injection.

Hypotension: Symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving TRANDATE Injection. Therefore, the patient's ability to tolerate an upright position should be established before permitting any ambulation.

Jaundice or Hepatic Dysfunction: On rare occasions, oral labetalol HCl has been associated with jaundice (both hepatic and cholestatic). It is therefore recommended that treatment with labetalol HCl be stopped immediately should a patient develop jaundice or laboratory evidence of liver injury. Both have been shown to be reversible on stopping therapy.
Information for Patients: The following information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects. During and immediately following (for up to 3 hours) TRANDATE Injection, the patient should remain supine. Subsequently, the patient should be advised on how to proceed gradually to become ambulatory, and should be observed at the time of first ambulation.

When the patient is started on TRANDATE Tablets, following adequate control of blood pressure with TRANDATE Injection, appropriate directions for titration of dosage should be provided (see **DOSAGE AND ADMINISTRATION**).

As with all drugs with beta-blocking activity, certain advice to patients being treated with labetalol HCl is warranted: While no incident of the abrupt withdrawal phenomenon (exacerbation of angina pectoris) has been reported with labetalol HCl, dosing with TRANDATE Tablets should not be interrupted or discontinued without a physician's advice. Patients being treated with TRANDATE Tablets should consult a physician at any sign of impending cardiac failure. Also, transient scalp tingling may occur, usually when treatment with TRANDATE Tablets is initiated (see **ADVERSE REACTIONS**).
Laboratory Tests: Routine laboratory tests are ordinarily not required before or after intravenous labetalol HCl. In patients with concomitant illnesses, such as impaired renal function, appropriate tests should be done to monitor these conditions.
Drug Interactions: Since TRANDATE (labetalol HCl) Injection may be administered to patients already being treated with other medications, including other antihypertensive agents, careful monitoring of these patients is necessary to detect and treat promptly any undesired effect from concomitant administration.

In one survey, 2.3% of patients taking labetalol HCl orally in combination with tricyclic antidepressants experienced tremor as compared to 0.7% reported to occur with labetalol HCl alone. The contribution of each of the treatments to this adverse reaction is unknown, but the possibility of a drug interaction cannot be excluded.

Drugs possessing beta-blocking properties can blunt the bronchodilator effect of beta-receptor agonist drugs in patients with bronchospasm; therefore, doses greater than the normal anti-asthmatic dose of beta-agonist bronchodilator drugs may be required.

Cimetidine has been shown to increase the bioavailability of labetalol HCl administered orally. Since this could be explained either by enhanced absorption or by an alteration of hepatic metabolism of labetalol HCl, special care should be used in establishing the dose required for blood pressure control in such patients.

Synergism has been shown between halothane anesthesia and intravenously administered labetalol HCl. During controlled hypotensive anesthesia using labetalol HCl in association with halothane, high concentrations (3% or above) of halothane should not be used because the degree of hypotension will be increased and because of the possibility of a large reduction in cardiac output and an increase in central venous pressure. The anesthesiologist should be informed when a patient is receiving labetalol HCl.

Labetalol HCl blunts the reflex tachycardia produced by nitroglycerin without preventing its hypotensive effect. If labetalol HCl is used with nitroglycerin in patients with angina pectoris, additional antihypertensive effects may occur.

Drug/Laboratory Test Interactions: The presence of a metabolite of labetalol HCl in the urine may result in falsely increased levels of urinary catecholamines when measured by a nonspecific trihydroxyindole (THI) reaction. In screening patients suspected of having a pheochromocytoma and being treated with labetalol HCl, specific radioenzymatic or high performance liquid chromatography assay techniques should be used to determine levels of catecholamines or their metabolites.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term oral dosing studies with labetalol HCl for 18 months in mice and for 2 years in rats showed no evidence of carcinogenesis. Studies with labetalol HCl, using dominant lethal assays in rats and mice, and exposing microorganisms according to modified Ames tests, showed no evidence of mutagenesis.
Pregnancy Category C: Teratogenic studies have been performed with labetalol HCl in rats and rabbits at oral doses up to approximately 6 and 4 times the MRHD, respectively. No reproducible evidence of fetal malformations was observed. Increased fetal resorptions were seen in both species at doses approximating the MRHD. There are no adequate and well-controlled studies in pregnant women. Labetalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nonteratogenic Effects: Infants of mothers who were treated with labetalol HCl for hypertension during pregnancy did not appear to be adversely affected by the drug. Oral administration of labetalol to rats during late gestation through weaning at doses of 2 to 4 times the MRHD caused a decrease in neonatal survival.
Labor and Delivery: Labetalol HCl given to pregnant women with hypertension did not appear to affect the usual course of labor and delivery.
Nursing Mothers: Small amounts of labetalol (approximately 0.004% of the maternal dose) are excreted in human milk. Caution should be exercised when TRANDATE (labetalol HCl) Injection is administered to a nursing woman.
Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS: TRANDATE® Injection is usually well tolerated. Most adverse effects have been mild and transient and, in controlled trials involving 92 patients, did not require labetalol HCl withdrawal. Symptomatic postural hypotension (incidence 58%) is likely to occur if patients are tilted or allowed to assume the upright position within 3 hours of receiving TRANDATE Injection. Moderate hypotension occurred in 1 of 100 patients while supine. Increased sweating was noted in 4 of 100 patients, and flushing occurred in 1 of 100 patients.

The following also were reported with TRANDATE Injection with the incidence per 100 patients as noted:

Cardiovascular System: Ventricular arrhythmia in 1.

Central and Peripheral Nervous Systems: Dizziness in 9; tingling of the scalp/skin in 7; hypoesthesia (numbness) and vertigo in 1 each.

Gastrointestinal System: Nausea in 13; vomiting in 4; dyspepsia and taste distortion in 1 each.

Metabolic Disorders: Transient increases in blood urea nitrogen and serum creatinine levels occurred in 8 of 100 patients; these were associated with drops in blood pressure, generally in patients with prior renal insufficiency.

Psychiatric Disorders: Somnolence/yawning in 3.

Respiratory System: Wheezing in 1.

Skin: Pruritus in 1.

The incidence of adverse reactions depends upon the dose of labetalol HCl. The largest experience is with oral labetalol HCl (see TRANDATE Tablet Product Information for details). Certain of the side effects increased with increasing oral dose as shown in the table below which depicts the entire U.S. therapeutic trials data base for adverse reactions that are probably or possibly dose-related.

Labetalol HCl Daily Dose (mg)	**200**	**300**	**400**	**600**	**800**	**900**	**1200**	**1600**	**2400**
Number of Patients	522	181	606	608	503	117	411	242	175
Dizziness (%)	2	3	3	3	5	1	9	13	16
Fatigue	2	1	4	4	5	3	7	6	10
Nausea	<1	0	1	2	4	0	7	11	19
Vomiting	0	0	<1	<1	<1	0	1	2	3
Dyspepsia	1	0	2	1	1	0	2	2	4
Paresthesias	2	0	2	2	1	1	2	5	5
Nasal Stuffiness	1	1	2	2	2	2	4	5	6
Ejaculation Failure	0	2	1	2	3	0	4	3	5
Impotence	1	1	1	1	2	4	3	4	3
Edema	1	0	1	1	1	0	1	2	2

The oculomucocutaneous syndrome associated with the beta-blocker practolol has not been reported with labetalol HCl during investigational use and extensive foreign marketing experience.
Clinical Laboratory Tests: Among patients dosed with TRANDATE Tablets, there have been reversible increases of serum transaminases in 4% of patients tested and, more rarely, reversible increases in blood urea.
OVERDOSAGE: Overdosage with TRANDATE® Injection causes excessive hypotension which is posture sensitive and, sometimes, excessive bradycardia. Patients should be laid supine and their legs raised if necessary to improve the blood supply to the brain. The following additional measures should be employed if necessary: **Excessive bradycardia**—administer atropine (3.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously. **Cardiac failure**—administer a digitalis glycoside and diuretic. **Hypotension**—administer vasopressors, eg, norepinephrine. There is pharmacological evidence that norepinephrine may be the drug of choice. **Bronchospasm**—administer a beta$_2$-stimulating agent and/or a theophylline preparation.

If overdosage with labetalol HCl follows oral ingestion, gastric lavage or pharmacologically induced emesis (using syrup of ipecac) is useful for removal of the drug shortly after ingestion. Labetalol HCl can be removed from the general circulation by hemodialysis.

The oral LD$_{50}$ value of labetalol HCl in the mouse is approximately 600 mg/kg and in the rat is greater than 2 g/kg. The intravenous LD$_{50}$ in these species is 50 to 60 mg/kg.
DOSAGE AND ADMINISTRATION: Initiation of Dosing with TRANDATE Tablets: Subsequent oral dosing with TRANDATE Tablets should begin when it has been established that the supine diastolic blood pressure has begun to rise. The recommended initial dose is 200 mg, followed in 6-12 hours by an additional dose of 200 mg or 400 mg, depending on the blood pressure response. Thereafter, **inpatient titration with TRANDATE Tablets** may proceed as follows:

Inpatient Titration Instructions

Regimen	Daily Dose*
200 mg bid	400 mg
400 mg bid	800 mg
800 mg bid	1600 mg
1200 mg bid	2400 mg

*If needed, the total daily dose may be given in three divided doses.

While in the hospital, the dosage of TRANDATE (labetalol HCl) Tablets may be increased at one-day intervals to achieve the desired blood pressure reduction.
HOW SUPPLIED: TRANDATE® Injection, 5 mg/ml, is supplied in 20 ml (100 mg) ampuls, box of 1 (NDC 0173-0350-59).
Store between 2° and 30°C (36° and 86°F). Do not freeze.

Glaxo

Manufactured for Glaxo Inc.
Research Triangle Park, NC 27709
by Schering Pharmaceutical Corporation (PR)
Manati, PR 00701
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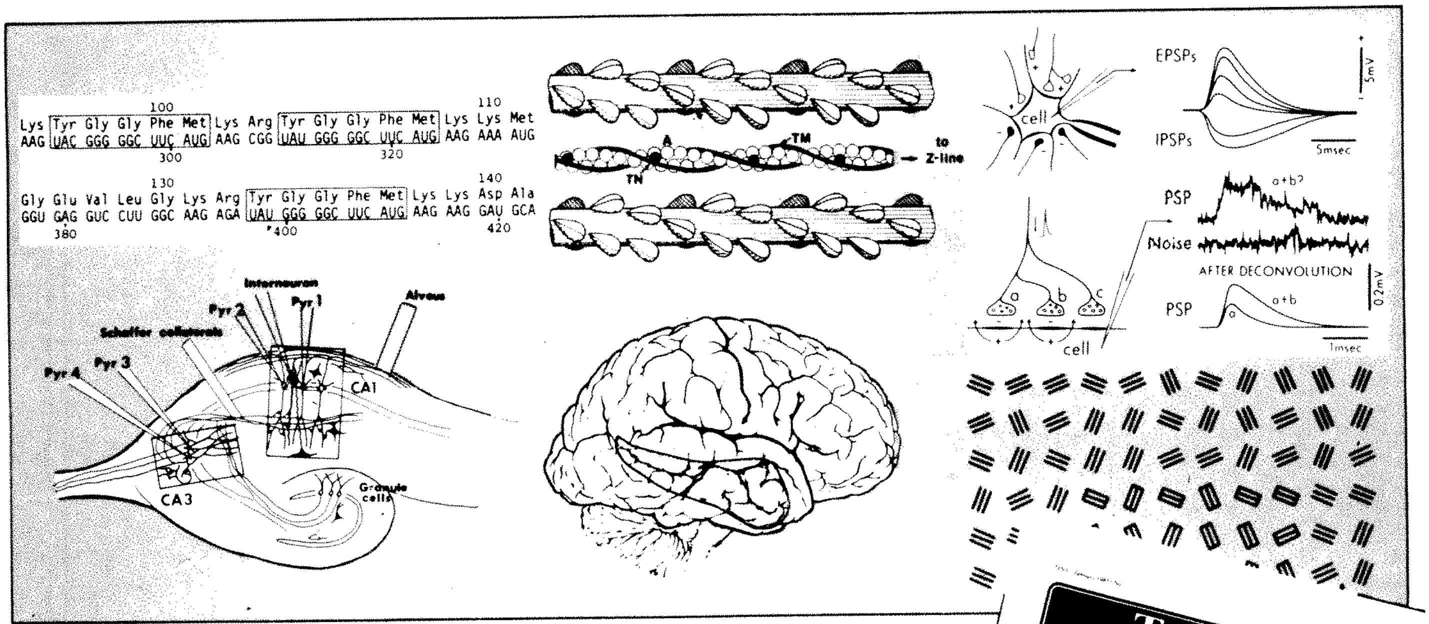
October 1984

Trends in NeuroSciences



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Schaffer collaterals
Pyr 3
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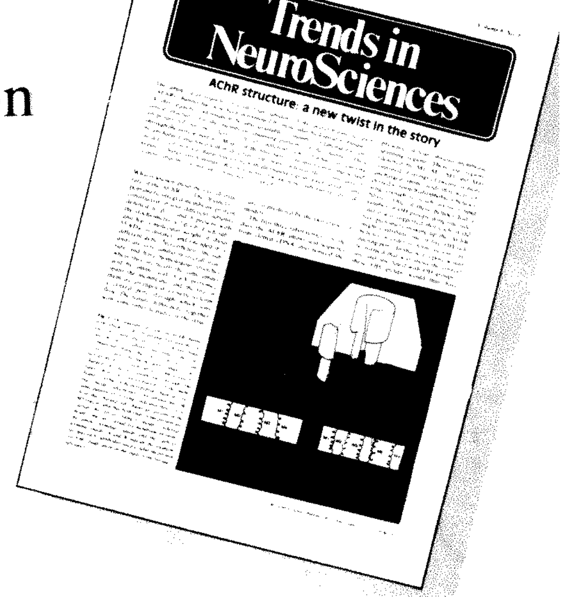
Granule cells

From genes to behaviour –the central connection


Trends in NeuroSciences

AChR structure: a new twist in the story

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The new technology has demonstrated the ability of a handful of gene products to orchestrate a complex sequence of behaviour in the marine mollusc *Aplysia*. Rapid progress is also being made in understanding how specific gene products control development in the insect's nervous system, or regulate the switching of transmitter production in adult mammalian neurons. Undoubtably molecular genetics will have a major impact on clinical neuroscience during the 1980s.

Gene research in neuroscience is not the only area where activities are occuring at an explosive rate. PET studies of human cognitive function, computer monitoring of whole body and limb movement and psychophysical testing of perceptual activities are all contributing to our knowledge of higher brain functions in health and disease.

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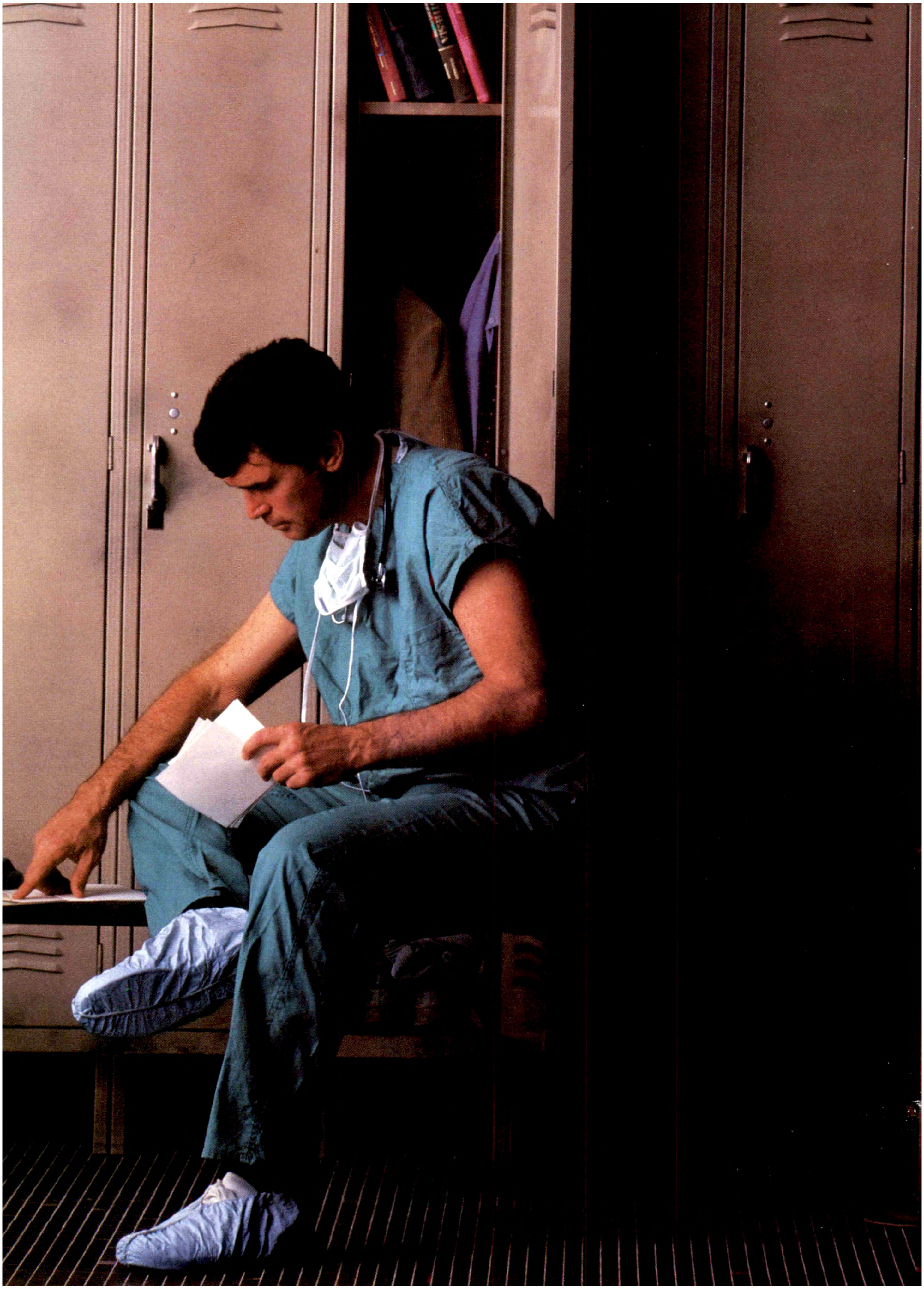

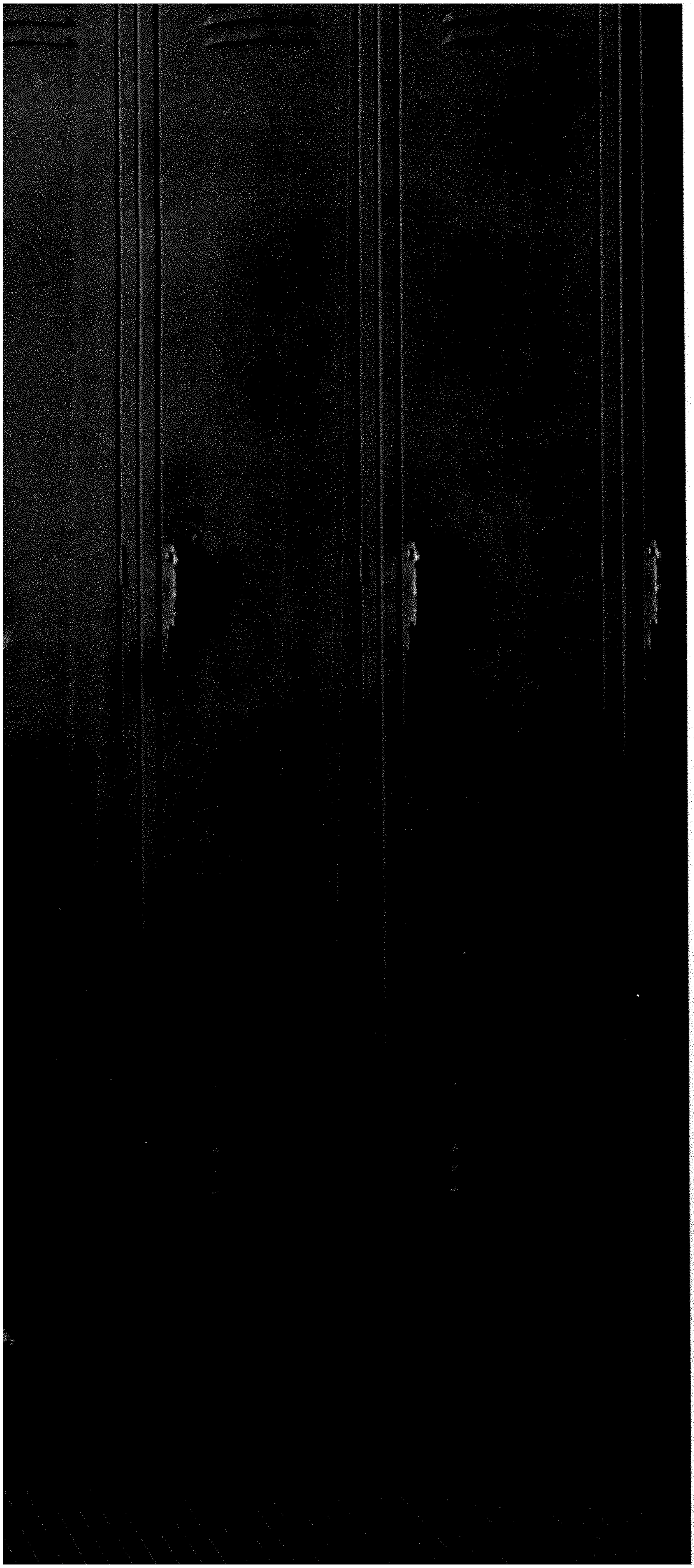

TWO D&Cs, AN ARTHROSCOPY, THREE TUBALS, AND A TUCK...

...day after day, outpatient surgery turns on the skills of the anesthesiologist. Which is why more and more anesthesiologists turn to STADOL® (butorphanol tartrate) for potent analgesia. Rapid onset (one minute IV) makes STADOL a good fit for most short procedures, and its 3 to 4 hour duration covers postoperative pain as well.[1,2] Respiratory depression, nausea and vomiting typically aren't STADOL problems.[3,4] Which means patients are discharged and surgeries begin...on schedule. But caution is advised in patients suspected of narcotic abuse, to avoid withdrawal syndrome.

From induction through early recovery, the STADOL outpatient remains pain-free and calm, yet still responsive. And there's minimal risk of rebound effects after discharge.

STADOL .03 mg/kg. A profile that helps you turn a busy schedule into a good day's work.

Please see next page for brief summary of prescribing information.

Stadol® IM IV

(butorphanol tartrate)

IN BY 9 OUT BY 3

REFERENCES

1. Pierce HE: An effective method of inducing analgesia and anesthesia for dermatoplastic surgery in an office. J Dermatol Surg Oncol 1981;7:495-496. /2. Cook TA: Butorphanol tartrate: An intravenous analgesic for outpatient surgery. Otolaryngol Head Neck Surg 1983;9:251-254. /3. Kallos T, Caruso FS: Respiratory effects of butorphanol and pethidine. Anaesthesia 1979;34:633-637. /4. Skaredoff MN, Viguera MG: Double-blind comparison of butorphanol and morphine in balanced anesthesia. Anesthesiology Review 1980;7(No. 10):36-39.

BRISTOL®

Stadol® (Butorphanol tartrate)
Brief Summary of Prescribing Information

For complete information, consult Official Package Circular.

(2)12/10/79

INDICATIONS AND USAGE—Stadol is recommended for the relief of moderate to severe pain. Stadol can also be used for preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of prepartum pain.

CONTRAINDICATIONS—Stadol should not be administered to patients who have been shown to be hypersensitive to it.

WARNINGS—Patients Physically Dependent on Narcotics: Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.

Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

Drug Dependence: Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure: Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

Cardiovascular Effects: Because Stadol increases the work of the heart, especially the pulmonary circuit, the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

PRECAUTIONS—Certain Respiratory Conditions: Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function: Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

Biliary Surgery: Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

Usage as a Preoperative or Preanesthetic Medication: Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.

Usage in Balanced Anesthesia: The use of pancuronium in combination with Stadol may cause an increase in conjunctival changes.

Usage in Pregnancy: The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient. Reproduction studies have been performed in rats, mice and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

Usage in Labor and Delivery: Safety to the mother and fetus following administration of Stadol during labor has been established. Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.

Usage in Nursing Mothers: The use of Stadol in lactating mothers who are nursing their infants is not recommended since it is not known whether this drug is excreted in human milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.

Usage in Children: Safety and efficacy in children below age 18 years have not been established.

ADVERSE REACTIONS—The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503,40%), nausea (82, 6%), clammy/sweating (76, 6%).

Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).

Other adverse reactions which may occur (reported incidence of less than 1%) are:

CNS: nervousness, unusual dreams, agitation, euphoria, hallucinations
Autonomic: flushing and warmth, dry mouth, sensitivity to cold
Cardiovascular: palpitation, increase or decrease of blood pressure
Gastrointestinal: vomiting
Respiratory: slowing of respiration, shallow breathing
Dermatological: rash or hives
Eye: diplopia or blurred vision

OVERDOSAGE—Manifestations: Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

Treatment: The immediate treatment of suspected Stadol overdosage is intravenous naloxone.

The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors and assisted or controlled respiration.

HOW SUPPLIED—Stadol (butorphanol tartrate) injection for I.M. or I.V. use, is available as follows:

NDC 0015-5644-20—2 mg per ml, 2-ml vial
NDC 0015-5645-20—1 mg per ml, 1-ml vial
NDC 0015-5646-20—2 mg per ml, 1-ml vial
NDC 0015-5646-23—2 mg per ml, 1-ml Disposable Syringe
NDC 0015-5648-20—2 mg per ml, 10-ml multi-dose vial

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Second Edition

Editors:

Eric R. Kandel, M.D.
The Howard Hughes Medical Institute, Center for Neurobiology and Behavior, College of Physicians and Surgeons, Columbia University

James H. Schwartz, M.D., Ph.D.
The Howard Hughes Medical Institute, Center for Neurobiology and Behavior, College of Physicians and Surgeons, Columbia University

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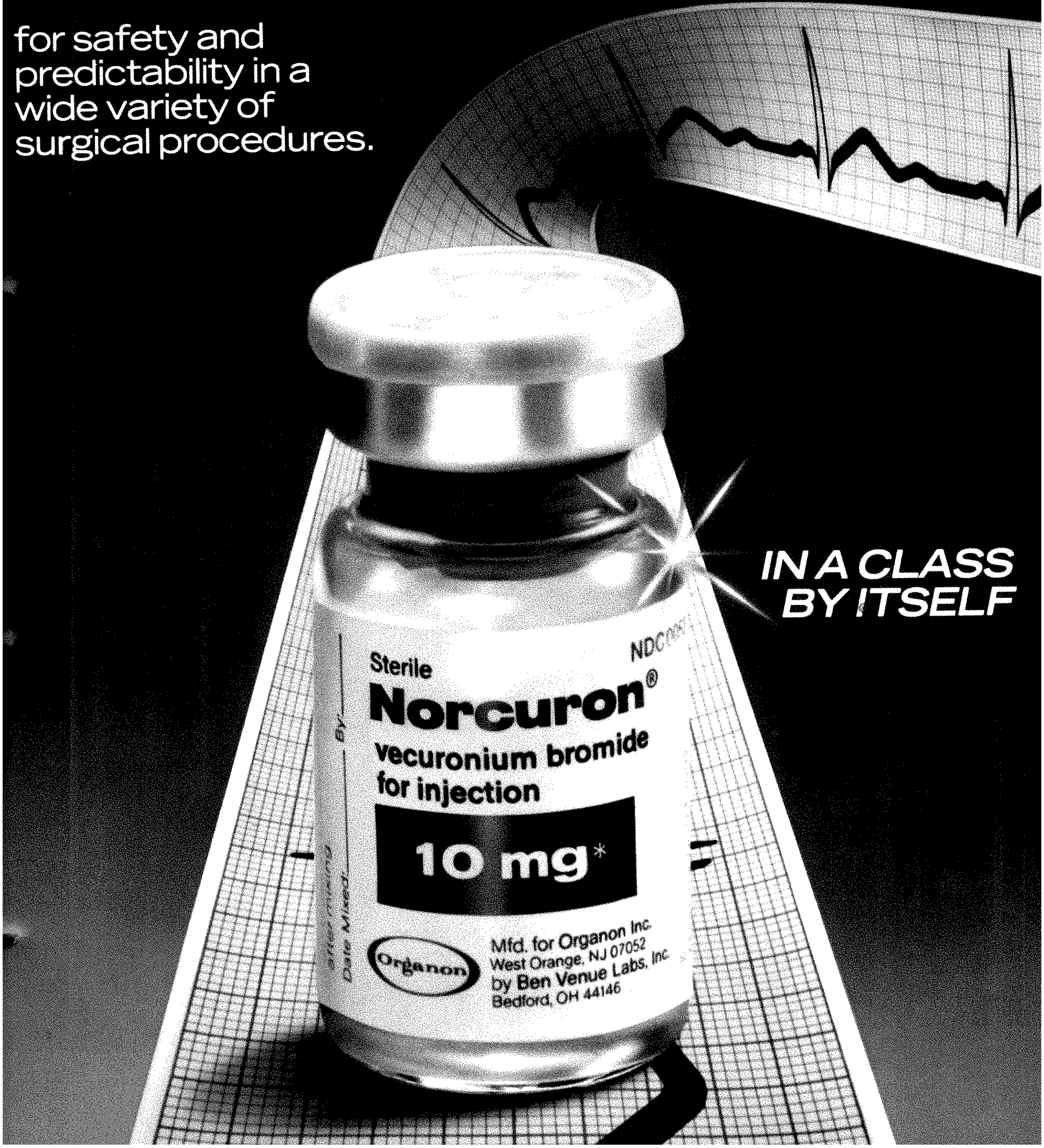

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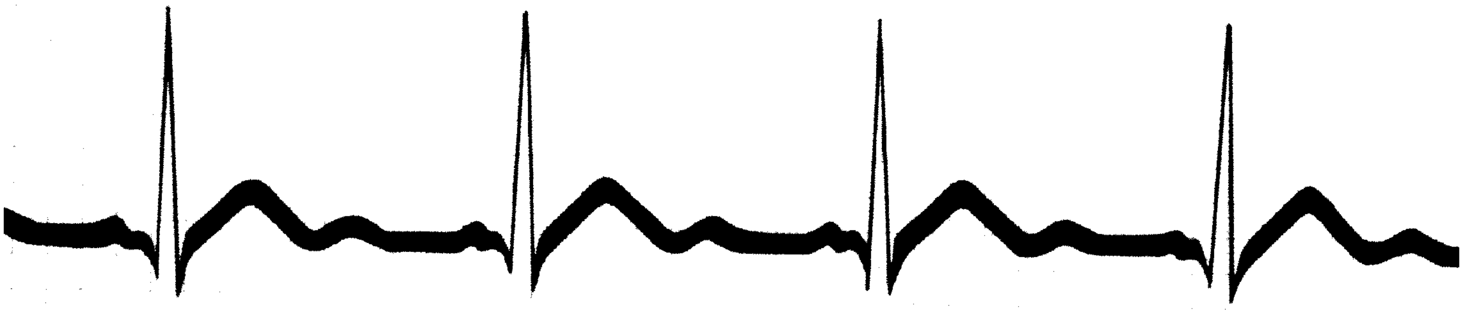

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(vecuronium bromide) injection

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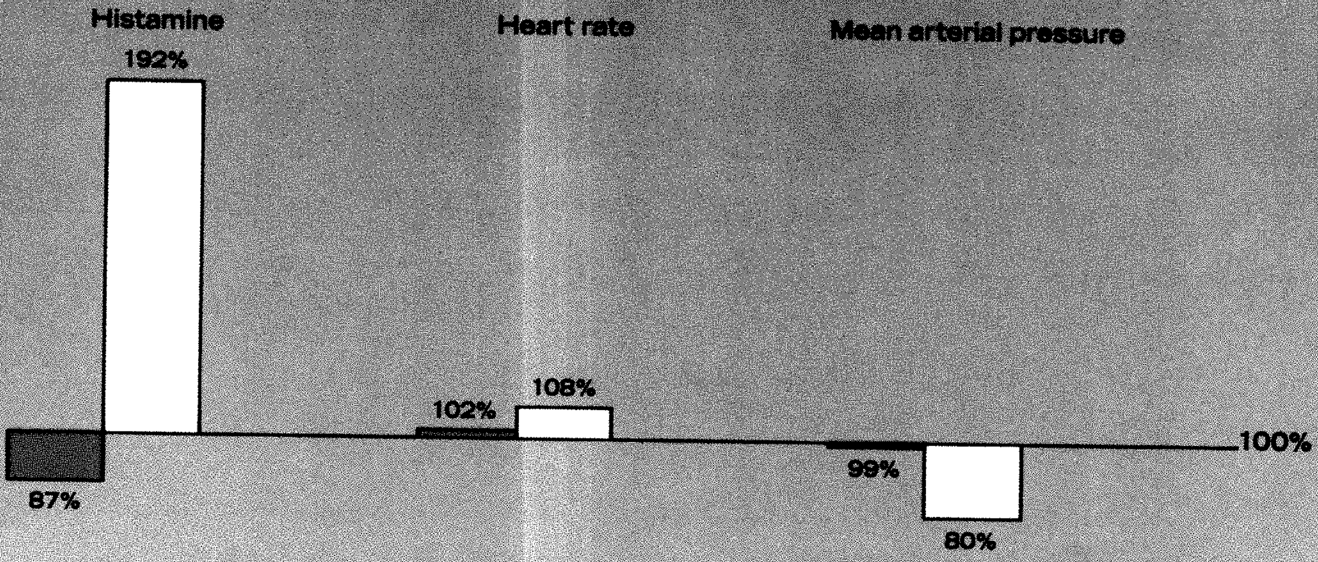
☐ does not produce clinically significant vagolytic or cardiodepressive effects[1,2,3]

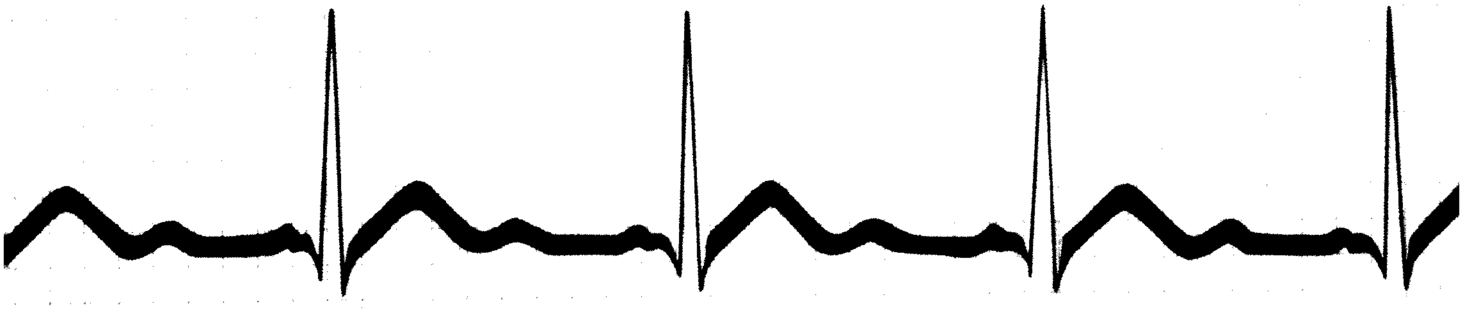
☐ indicated for cardiac surgery: coronary artery bypass grafting[1,4]

☐ indicated for patients with underlying cardiovascular problems undergoing various surgical procedures

Histamine release unlikely to occur[5]



	Drug	Dose (mg/kg)	*n*	× ED_{95}
☐	Atracurium	0.6	10	3
▨	Vecuronium	0.2	8	3.5



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For predictability

- ☐ may be used alone for intubation within 2½ to 3 minutes
- ☐ lacks clinically important cumulative effects

Indicated for:

- ☐ procedures lasting 25 minutes or longer
- ☐ the patient with asthma
- ☐ outpatient surgery
- ☐ pediatrics (infants seven weeks or older)

Before you decide, consider:

NORCURON® (vecuronium bromide) injection	
Histamine release	unlikely to occur
Cardiovascular effects	none clinically significant
Refrigeration	not required; stable at room temperature
Potency	reliably activated upon demand
Metabolites	3-deacetyl vecuronium
Usage in infancy	yes: seven weeks or older

NORCURON®

IN A CLASS BY ITSELF

References 1. Morris RB, Cahalan MK, Miller RD, et al: The cardiovascular effects of vecuronium (ORG NC45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 58:438-440, 1983. 2. Krieg N, Crul JF, Booij LH: Relative potency of ORG NC45, pancuronium, alcuronium and tubocurarine in anaesthetized man. *Br J Anaesth* 52:783-788, 1980. 3. Lienhart A, Guggiari M, Maneglia R, et al: Cardiovascular effects of vecuronium in man, in Agoston S et al (eds): *Clinical Experiences with Norcuron® (Org NC 45, Vecuronium Bromide)* (Symposium Geneva, 21-22 April, 1983). Current Clinical Practice Series 11, Amsterdam, Excerpta Medica, 1983, pp 150-155. 4. Gallo JA, Fries E, et al: Hemodynamic effects of bolus injection of vecuronium in cardiac surgical patients. *Anesthesiology* 61:A63, 1984. 5. Basta SJ, Savarese JJ, Ali HH, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 59:A273, 1983.

See next page for complete prescribing information.

ORCURON®

(vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON* (vecuronium bromide injection) is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2 ß, 3α, 5α, 16ß, 17ß)-3,17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide. The structural formula is:

Norcuron* is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron* (vecuronium bromide injection) is a nondepolarizing neuromusular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron* is about ⅓ more potent than pancuronium, the duration of neuromuscular blockade produced by Norcuron* is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron* doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED_{90} (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron* dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron* is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron* is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron* may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron* and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron* will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron*, the administration of Norcuron* should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron* has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron* has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron* neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron* is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron* induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron* is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron* varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron* (vecuronium bromide injection) has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron*; equipotent doses are of approximately the same duration as Norcuron* in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron* within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron*. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron* in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of Norcuron* during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

NO REFRIGERATION REQUIRED

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron* has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron* is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: None known.

WARNINGS: NORCURON* SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron* may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: Renal Failure: Norcuron* is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron* should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron* metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTENT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron*.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron* is capable of triggering malignant hyperthermia.

Norcuron* has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron* (vecuronium bromide injection) and its duration of action. If succinylcholine is used before Norcuron*, the administration of Norcuron* should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron* may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron* before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the sam fashion as does Norcuron*; therefore these drugs and Norcuron* may manifest an additive effect when used together. There ar insufficient data to support concomitant use of Norcuron* and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron* wi enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents th initial dose of Norcuron* may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered fc a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscul block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such a neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; an sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron* during surger unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrer paralysis may occur. This possibility must also be considered for Norcuron*. Norcuron* induced neuromuscular blockade ha been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases whic lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Dependin on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for th management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/laboratory test interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluat carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron*. It is also not know whether Norcuron* can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately mor sensitive to Norcuron* on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently availabl does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron* was well-tolerated and produced no adverse reactions during extensive clinical trials. The mos frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacologica action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound an prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron* as with all curarifor drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or n increase in intensity of blockade or duration of action of Norcuron* is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron* overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron* can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron* as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol* (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron*. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron* (vecuronium bromide injection) is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron* by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron* and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron* is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron* is enhanced. If Norcuron* is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron* dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron*. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron* to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron* are recommended; after the initial Norcuron* injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron* lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron* on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

COMPATIBILITY: Norcuron* is compatible in solution with:

- 0.9% NaCl solution
- 5% glucose in water
- 5% glucose in saline
- Lactated Ringers

HOW SUPPLIED: 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent.
Boxes of 10. NDC # 0052-0442-17

STORAGE: PROTECT FROM LIGHT. Store at 15°-30°C (59°-86°F).

AFTER RECONSTITUTION: Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS.

DISCARD UNUSED PORTION.

SINGLE USE VIALS.

PTD. IN USA-442

ISSUED 3/85

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ANESTH ANALG
1986;65:431–6

Regional and Global Myocardial Function in the Dog when Nitrous Oxide Is Added to Halothane in the Presence of Critical Coronary Artery Constriction

James G. Ramsay, BSc, MD, Charles C. Arvieux, MD, Pierre Foëx, MD, DPhil,
Daniel M. Philbin, MD, Peter Jeavons, BA, W. Alan Ryder, and Lee A. Jones

RAMSAY JG, ARVIEUX CC, FOËX P, PHILBIN DM, JEAVONS P, RYDER WA, JONES LA. Regional and global myocardial function in the dog when nitrous oxide is added to halothane in the presence of critical coronary artery constriction. 1986;65:431–6.

The effect of substituting 66% nitrous oxide for nitrogen on global and regional myocardial function before and after critical constriction of the left anterior descending coronary artery (LAD) was studied in six open-chested dogs anesthetized with 1% halothane (inspired). Regional myocardial function was measured in the region of the LAD and in the region of the left circumflex artery using sonomicrometry, and LAD blood flow was measured. Administration of nitrous oxide produced moderate depression of global performance. Regional shortening in both myocardial segments was reduced, and dysfunction also appeared in the LAD segment. This dysfunction was observed in the presence of both normal coronary blood flow, and after critical constriction. The appearance of dysfunction when coronary blood flow was unimpaired suggests that ischemia may not be the only cause of regional myocardial dysfunction.

Key Words: HEART—coronary heart disease, ventricular function. ANESTHETICS, GASES—nitrous oxide.

Postsystolic shortening appears in the canine left ventricle when nitrous oxide is added to fentanyl or sufentanil anesthesia in the presence of critical coronary artery constriction (1). This abnormal contraction pattern suggests regional ischemic dysfunction, even though it occurs in the absence of significant changes in coronary flow or perfusion pressure. This study was undertaken to see whether nitrous oxide added to halothane would result in similar regional dysfunction.

Methods

Six mongrel dogs weighing 20 ± 0.8 kg (mean ± SEM) were studied. After morphine premedication (2 mg/kg) anesthesia was induced with thiopental, 10 mg/kg, and the trachea was intubated. Mechanical ventilation was instituted with an inspired gas mixture of 33% oxygen, nitrogen, and sufficient carbon dioxide to maintain normocarbia. Anesthesia was maintained with halothane (1–2% inspired, Fluotec vaporizer). Normothermia was ensured by a servocontrolled heating element incorporated into the operating table, and a sensor placed in the midesophagus.

After insertion of a 14-gauge cannula in the left carotid artery for measurement of arterial pressure (Statham pressure transducer), insertion of an intravenous cannula for administration of normal saline at 4 ml·kg^{-1}·hr^{-1}, and attachment of standard limb leads to monitor lead II of the electrocardiogram, a left thoracotomy was performed excising the fifth and sixth ribs. The heart was exposed and suspended in a pericardial cradle, and a catheter was placed in the pulmonary artery under direct vision for measurement of cardiac output by dye dilution (indocyanin green). A stiff cannula was placed through the apical dimple of the left ventricle for measurement of pressure (Statham pressure transducer) and its first derivative (dP/dt). A flow transducer (SEM 230, SE Laboratories) was placed around the root of the aorta for measurement of flow, its first derivative (acceleration), and its integral (stroke volume).

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Address correspondence to Dr. Ramsay, Department of Anaesthesia, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec, Canada H3A 1A1.

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Table 1. Experimental Protocol

Halothane 1%, O_2 33%, N_2 or N_2O 66%[a]	
N_2	15 min
N_2O	15 min
N_2	15 min
N_2O	15 min
N_2	15 min
Critical constriction of the LAD	
N_2	15 min
N_2O	15 min
N_2	15 min
N_2O	15 min
N_2	15 min

Abbreviation: LAD, left anterior descending coronary artery.
[a] CO_2 added to maintain normocarbia.

The left anterior descending coronary artery (LAD) was dissected free distal to the first diagonal branch, and a flow transducer (SEM 230, SE Laboratories) placed around it. A micrometer-controlled snare was placed distal to the flow transducer for application of critical constriction.

Two pairs of piezoelectric crystals were inserted in the subendocardium for measurement of regional myocardial function. The crystals were placed at right angles to the long axis of the heart, one pair in the area near the apex supplied by the LAD, and another pair high on the anterior wall in an area supplied by the left circumflex artery (LC). The technique of insertion of the crystals and the principles of length measurement using sonomicrometry have been previously described (2,3).

Approximately 4 hr after the start of anesthesia and at least 1 hr after placement of all monitoring devices, and after verification of normal acid–base balance, normocarbia, and normal left ventricular filling pressure, the study protocol was begun. While inspired halothane concentration was maintained at 1%, and inspired oxygen at 33% (Taylor Servomex Oxygen Analyser, Type OA 272, Taylor Instrument Ltd., Crowborough, Sussex, England), nitrous oxide replaced nitrogen for two 15-min periods. Recordings were made as indicated in Table 1. Critical constriction of the LAD was then applied, using the micrometer-controlled snare. The snare was tightened in such a way that although regional function was unaltered, the hyperemic response that normally follows a 10-sec complete occlusion of the artery was abolished. Previous experience has shown that this procedure reduces flow by approximately 30% (4). Exposure to nitrous oxide was then repeated in the same sequence as before the application of critical constriction (Table 1).

Signals were recorded on a Mingograph 81 eight channel recorder (Elema Schonander, Stockholm, Solna, Sweden). Calibrations for aortic flow, stroke volume (the integral of aortic flow), and aortic blood acceleration (the first derivative of aortic flow) were made by simultaneous determinations of cardiac output. Regional shortening was timed in relation to global indices; end-diastole was defined as the onset of left ventricular dP/dt, and end-systole as the time when the aortic flow signal first returned to zero. Regional shortening that occurred after end-systole was "postsystolic."

At the termination of the experiment the coronary flow transducer was calibrated with known volumes of blood. The LAD was then injected with blue ink to determine the mass of ventricular muscle supplied, for calculation of coronary blood flow per 100 g of tissue. The data were manually digitized, derived hemodynamic variables were obtained using standard formulas, and results were analyzed using Student's paired t-test, with $P < 0.05$ as the requirement for statistical significance.

Results

Blood gas tensions were normal in all dogs. All results are based on 12 nitrous oxide challenges in six dogs, except for coronary blood flow after critical constriction. For this measurement, the recordings of three challenges were inadequate because of baseline drift. Therefore nine challenges (in five dogs) are included in the coronary blood flow analysis for this time period. Results are expressed as mean ± SEM.

Before Critical Constriction

Global function. The effects of nitrous oxide on global function are summarized in Table 2. The addition of nitrous oxide to halothane resulted in no significant change in heart rate, left ventricular end diastolic pressure (LVEDP), or systemic vascular resistance (SVR). Small but statistically significant reductions in mean arterial pressure and coronary perfusion pressure (diastolic blood pressure minus LVEDP) occurred. Coronary blood flow was not significantly affected. All the measured indices of left ventricular (LV) performance, maximum LV dP/dt, peak aortic blood acceleration, peak LV power, and cardiac output, were significantly reduced by nitrous oxide.

Regional function. Nitrous oxide administration resulted in small increases in the end diastolic length (EDL) of both the LAD segment (from 12.6 ± 0.4 to 12.8 ± 0.4 mm; $P < 0.05$), and the LC segment (from 11.5 ± 0.6 to 11.8 ± 0.6 mm; $P < 0.05$). There was

Table 2. The effect of N_2O on Global Cardiac Function: 12 Challenges in Six Dogs

	Preconstriction		Postconstriction	
	N_2	N_2O	N_2	N_2O
Heart rate (beats/min)	103.3 ± 6.4	110.2 ± 4.3	115.0 ± 7.3	115.3 ± 4.5
Mean arterial pressure (mm Hg)	91.6 ± 2.1	84.6 ± 2.8[a]	95.3 ± 2.3	86.8 ± 2.4[a]
LVEDP (mm Hg)	5.2 ± 0.5	5.9 ± 0.3	4.9 ± 0.3	5.8 ± 0.5[a]
Coronary perfusion pressure (mm Hg)	77.3 ± 2.2	70.6 ± 3.3[a]	81.6 ± 2.6	72.4 ± 2.7[a]
LV dP/dt maximum (mm Hg/sec)	1500 ± 74	1217 ± 55[a]	1446 ± 46	1192 ± 30[a]
Aortic blood acceleration (ml/sec)	4444 ± 298	3379 ± 184[a]	4016 ± 235[b]	3043 ± 178[a]
Peak LV Power (mW)	2290 ± 136	1730 ± 68[a]	2033 ± 103[b]	1589 ± 67[a]
Cardiac output (ml/min)	1714 ± 78	1490 ± 45[a]	1565 ± 56	1377 ± 65[a]
Coronary blood flow ($ml \cdot min^{-1} \cdot 100\ g^{-1}$)	54.4 ± 4.2	61.1 ± 5.0	39.4 ± 3.7[b,c]	33.5 ± 4.0[a,c]
Systemic vascular resistance ($dynes/cm^5$)	4368 ± 209	4577 ± 185	4951 ± 258[b]	5172 ± 280

All results are mean ± SEM.
Abbreviations: LVEDP, left ventricular end diastolic pressure; LV, left ventricle.
[a]Indicates $P < 0.05$ vs N_2.
[b]Indicates $P < 0.05$ vs preconstriction N_2.
[c]Indicates $n = 9$ (see results).

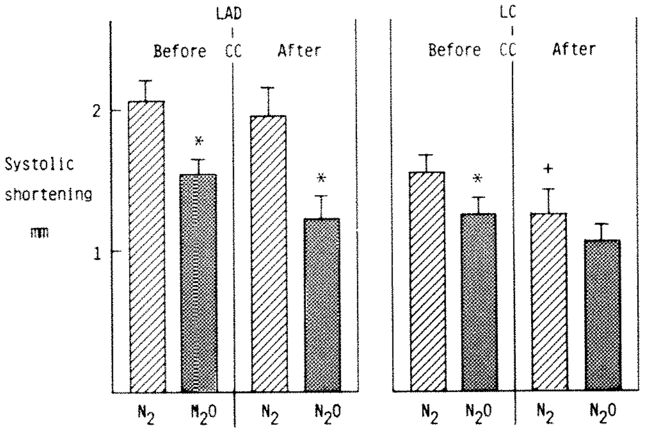

Figure 1. The effect of nitrous oxide on regional shortening in the LAD and LC segments. CC, critical constriction of the LAD. *Indicates $P < 0.05$ vs the N_2 value; + indicates $P < 0.05$ vs the preconstriction N_2 value.

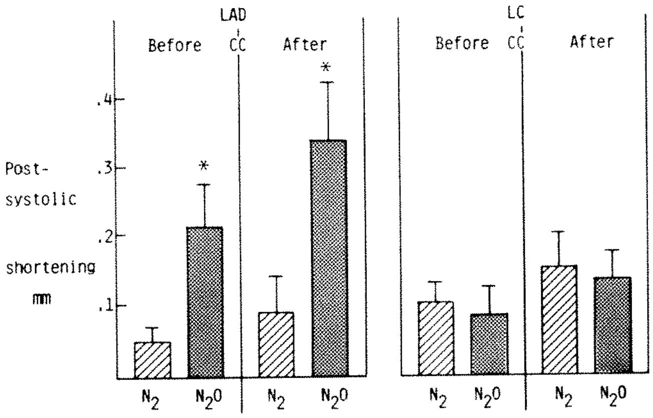

Figure 2. The effect of nitrous oxide on postsystolic shortening in the LAD and LC segments. Symbols and abbreviations as in Figure 1.

a significant reduction in systolic shortening in both segments (Fig. 1). Postsystolic shortening (shortening occurring after the end of ejection) was significantly increased in the LAD segment as illustrated in Figure 2. The small amount of postsystolic shortening present in the LC segment in the control state was unchanged by nitrous oxide (Fig. 2).

Effects of Critical Constriction

Application of critical constriction of the LAD resulted in a 28% reduction in LAD coronary blood flow, in keeping with previous experience (4). There were small reductions in peak LV power and aortic blood acceleration but not in maximum LV dP/dt, and there was also a significant increase in systemic vascular resistance. Other indices of global function were not affected. Regional function was unchanged apart from a small decrease in systolic shortening in the LC segment.

After Critical Constriction

Global function. The response after constriction paralleled that seen before constriction. Administration of nitrous oxide resulted in significant reductions in blood pressure, coronary perfusion pressure, and the indices of LV performance. In addition, LVEDP increased slightly but significantly, and coronary blood flow also decreased significantly (Table 2).

Regional function. A small but significant increase in end diastolic length occurred in the LAD segment when nitrous oxide was administered (from 12.6 ±

0.3 to 12.9 ± 0.4 mm), associated with a significant reduction in systolic shortening (Fig. 1). Postsystolic shortening increased significantly with nitrous oxide in this segment, as it did before critical constriction (Fig. 2). In the LC segment, also as before critical constriction, there was a small increase in EDL (from 11.4 ± 0.6 to 11.7 ± 0.6 mm; $P < 0.05$) and a reduction in systolic shortening, but the postsystolic shortening already present in the control state was not significantly affected by nitrous oxide.

Discussion

Our results indicate that the addition of 66% nitrous oxide to approximately 1 MAC halothane in the dog results in a significant reduction in global performance of the left ventricle, and in regional dysfunction in the LAD (apical) segment. Both of these effects appear whether the arterial supply to the apical region is normal or reduced.

Sixty-six percent nitrous oxide was substituted for nitrogen in the protocol in order to be comparable to the concentration likely to be employed in the clinical setting. This concentration of nitrous oxide is equivalent to approximately one third of an MAC in the dog (5). Although the effect of an "equivalent" increase in the halothane concentration was not examined, previous work from this laboratory has demonstrated that although increasing halothane results in increasing depression of performance, dysfunction appears only in the distribution of a critically constricted vessel, at high inspired concentrations (3,4).

The modest reduction in global performance with nitrous oxide is in keeping with previous findings in anesthetized dogs. Lundborg et al. (6) found a 10% decrease in LV dP/dt and stroke work, but little change in cardiac output when nitrous oxide was administered under halothane anesthesia, whereas Thorburn et al. (7) found an 11% decrease in cardiac output under pentobarbital anesthesia. The present findings of a 13% decrease in cardiac output, and a reduction of approximately 20% in indices of contractility (LV dP/dt, peak aortic blood acceleration, and peak LV power) are thus not surprising.

The lack of a major effect of nitrous oxide on preconstriction LAD blood flow is also consistent with previous findings, both in this laboratory (1) and elsewhere (7). In choosing a sample size of 12 (six dogs, two nitrous oxide administrations) and accepting a 5% risk of a type I error, we have accepted a greater risk of type II error (not finding a difference where one exists). With a small sample size and a difference between means that is only a moderate proportion of the sample standard deviation, the power of the analysis to detect a true effect is diminished. Although this does not reduce the strength of our positive findings, our negative results (such as the effect of nitrous oxide on LAD blood flow before critical constriction) may reflect smaller differences that a larger sample might have detected.

The reduction in LAD blood flow that occurred when nitrous oxide was added after critical constriction is an expected effect of the reduction in coronary perfusion pressure. When a coronary vessel has been critically constricted, flow through it is closely related to the driving pressure.

There were considerable differences in the effects of nitrous oxide on the two regions of the left ventricle studied, as indicated by the greater reductions in systolic shortening that occurred in the LAD segment with nitrous oxide, and the appearance of significant dysfunction when little effect was observed in the LC segment. We have observed a similar regional difference in effect when verapamil was administered in the presence of isoflurane (8). Other investigators have found less shortening at the base than at the apex of the heart, and that the apex maintains shortening in response to a transient increase in afterload better than the base (9). Regional differences in shortening have also been found in the normal human left ventricle (10).

In the control state there was slightly more postsystolic shortening in the LC than the LAD segment. In placing the crystals, efforts were made to select positions where there was little or no postsystolic shortening; however, near the base of the heart we consistently observed a small amount of postsystolic shortening in the control state (usually less than 5% of total shortening).

The apical dysfunction that occurred with nitrous oxide both before and after critical constriction of the LAD is in contrast to the study by Philbin et al. (1). In the latter study, postsystolic shortening occurred only after critical constriction of the LAD, leading the authors to implicate ischemia as the underlying mechanism. Our finding of dysfunction prior to critical constriction when flow was not reduced makes it difficult to invoke a similar mechanism. This does not preclude the possibility of redistribution of flow away from the endocardium, resulting in subendocardial ischemia as a result of increased wall stress and reduced perfusion pressure. However, the changes in these latter parameters before critical constriction were of such small magnitude that we do not believe they can explain dysfunction occurring in the presence of normal blood flow.

We have observed development of postsystolic shortening during graded application of coronary constriction (11), during deep halothane anesthesia in the presence of critical constriction (3), and most recently when nitrous oxide was added to narcotics in the presence of critical constriction (1). A similar pattern of dysfunction was found to develop in and near myocardial segments supplied by a stenotic coronary artery in response to isoproterenol infusion (12). Apart from our report of dysfunction developing when verapamil was given in the presence of isoflurane (8) and studies in which calcium antagonists were injected into coronary arteries directly (13), we are not aware of any report of regional dysfunction developing in the absence of obvious myocardial ischemia.

Figure 3 illustrates the abnormal pattern of shortening we observed, indicating segmental contraction (shortening) continuing to occur after the end of ejection (as indicated by the stroke volume tracing). As discussed above, some regions of the myocardium may normally show a small degree of this shortening pattern. The left ventricle is not a perfect sphere and regional changes in conformation undoubtedly occur, especially in the early ("isovolumic") phases of both systole and diastole. However, the appearance of a change in the pattern of shortening, such that systolic shortening is reduced and postsystolic shortening either appears de novo, or is greatly increased, indicates that differences in regional contraction are being magnified. Completely paradoxical wall motion (that is, systolic lengthening followed by shortening during diastole) which occurs in frank ischemia has been explained in terms of passive stretch followed by elastic recoil; however, postsystolic shortening or active contraction continuing into diastole is more difficult to explain. One possibility is that the region exhibiting postsystolic contraction is depressed compared to adjacent regions, and completion of its contraction is only possible once the stronger adjoining muscle has begun to relax.

If such regional dysfunction were simply the result of myocardial depression affecting the apical and basal segments differently, then we might expect any myocardial depressant to result in increasing degrees of postsystolic shortening in the apical region. This is not the case. Previous investigations in this laboratory have found regional dysfunction associated with increasing degrees of myocardial depression only when the coronary artery supplying the region was critically constricted (3,4). Clearly the addition of nitrous oxide to halothane has a different effect from an increase in halothane concentration alone.

We have recently reported regional dysfunction affecting the apical region more than the basal region, in the absence of transmural ischemia, when intravenous verapamil was administered during isoflurane

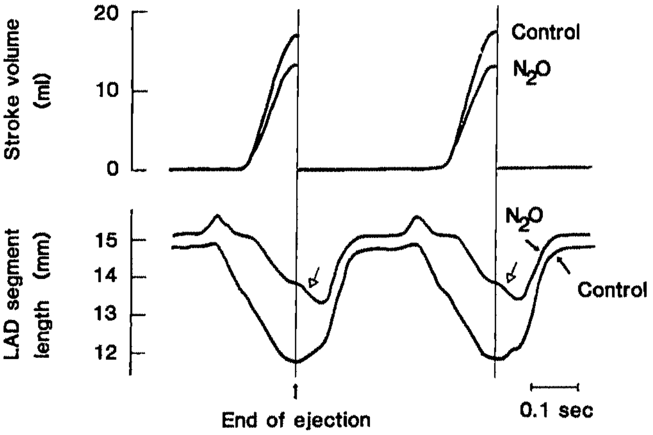

Figure 3. The shortening pattern induced by nitrous oxide in dog number 1 before critical constriction. The control and nitrous oxide recordings have been superimposed. Note that coincident with the reduction in stroke volume (upper trace) there is dilatation indicated by the rise in end-diastolic length, reduced systolic shortening, and continuation of shortening into the diastolic period (open arrows).

anesthesia (8). It is possible (though speculative) that the addition of two drugs that are known to affect calcium fluxes might result in a delay in the excitation–contraction coupling, resulting in dyssynchronous contraction as well as potent depression. Preexisting differences in regional contraction discussed above might make the apical region more sensitive to such an effect. Because the depressant effect of nitrous oxide can be reversed by calcium (14), and the negative inotropy caused by halothane may be partly a result of its effect on calcium fluxes (15,16), a similar mechanism may conceivably operate with halothane–nitrous oxide. Normal function when nitrous oxide is administered in the presence of narcotics and normal coronary blood supply is consistent with this hypothesis.

The implications of this study for the anesthetic management of patients with coronary artery disease are twofold, although extrapolation from canine studies to humans must be done with caution. First, nitrous oxide clearly induces reductions in both global and regional function of the left ventricle. More importantly, this agent can induce dysfunction, even in a normal area of the myocardium. Many patients with coronary artery disease have regions of the myocardium with diminished function, and administration of an agent known to induce dysfunction might be expected to worsen the degree of abnormality already present; in fact, patients with coronary artery disease have been reported to be particularly sensitive to the effects of nitrous oxide (17,18). These clinical reports, the results of Philbin et al. (1), and our present findings suggest that the routine administration of nitrous oxide in the patient with coronary artery disease must be questioned.

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Thiopental and Epinephrine-Induced Dysrhythmias in Dogs Anesthetized with Enflurane or Isoflurane

John L. Atlee III, MD, and Fred L. Roberts, MB, ChB, FFARCS

ATLEE JL III, ROBERTS FL. Thiopental and epinephrine-induced dysrhythmias in dogs anesthetized with enflurane or isoflurane. Anesth Analg 1986;65:437–43.

Epinephrine-induced dysrhythmias were studied in 19 dogs anesthetized with 1.25 MAC enflurane or isoflurane, or the same preceded by thiopental (20 mg/kg). In 11 (group 1) dogs, thiopental reduced the dose of epinephrine required for production of ventricular ectopy, bigeminy and tachycardia with enflurane, and only ventricular tachycardia with isoflurane ($P < 0.05$). Thiopental potentiation of epinephrine-induced dysrhythmias with enflurane lasted 4 hr after induction. In eight (group 2) dogs, the arrhythmic dose (ADE in μg/ml) and plasma level of epinephrine (PLE in ng/ml) for four or more ventricular extrasystoles in 15 sec were determined in the same animal under each of the four test conditions. ADE and PLE values ($\bar{X}$ ± SEM) were, respectively, enflurane, 9.1 ± 1.0 and 141 ± 24 (8/8 dogs); enflurane–thiopental, 5.0 ± 0.6 and 63 ± 16 (8/8 dogs); isoflurane, 28.3 and 330 (1/7 dogs); and isoflurane–thiopental, 15.2 ± 2.8 and 265 ± 59 (5/7 dogs). In addition, thiopental had no effect on plasma epinephrine levels reached during epinephrine infusions with 1.0 (enflurane only), 2.0 (enflurane, isoflurane) and 4.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (isoflurane only). Nor were epinephrine levels reached during enflurane or enflurane–thiopental different from those reached during isoflurane or isoflurane–thiopental. It is concluded that thiopental potentiates several types of epinephrine-induced ventricular dysrhythmias with enflurane, but only ventricular tachycardia with isoflurane. Furthermore, isoflurane or isoflurane–thiopental were less sensitizing than enflurane or enflurane–thiopental. Finally, neither thiopental nor the anesthetic agents affected plasma epinephrine levels reached during epinephrine infusions lasting 3 min.

Key Words: ANESTHETICS, INTRAVENOUS—thiopental. ANESTHETICS, VOLATILE—enflurane, isoflurane. HEART, ARRHYTHMIAS—electrocardiography.

Induction of anesthesia with thiopental in dogs reduces the dose of epinephrine required for production of ventricular dysrhythmias during both cyclopropane (1) and halothane anesthesia (2), an effect that persists up to 4 hr after induction. However, the effect of thiopental on epinephrine dysrhythmias with enflurane and isoflurane anesthesia has not been reported but is of some interest because thiopental is also used to facilitate induction with these agents. Additionally, enflurane and isoflurane appear to be less sensitizing than halothane in both humans (3) and animals (4,5).

In the present study, we examined the effect of induction with thiopental on epinephrine-induced dysrhythmias in dogs anesthetized with enflurane or isoflurane. As in the study with thiopental and halothane (2), graded infusions of epinephrine were used so that the dose of epinephrine for initiation of supraventricular and lesser ventricular dysrhythmias—those appearing before ventricular tachycardia during the course of sensitization—could be determined. Also, plasma levels of epinephrine at the time of ventricular dysrhythmias were determined in a separate group of dogs anesthetized with enflurane or isoflurane, either alone or after induction with thiopental.

Methods

All procedures performed conform with the *Guiding Principles in the Care and Use of Animals,* approved by the Council of the American Physiologic Society. Nineteen unpremedicated mongrel dogs of either sex (weight 12–20 kg) were fasted overnight and then anesthetized either with an inhalation induction (enflurane, isoflurane) or with intravenous thiopental (20 mg/kg). After induction, the trachea was intubated and the dogs mechanically ventilated (V_T 20–25 ml/kg) with enflurane or isoflurane in oxygen (F_{IO_2} 1.0) to

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Address correspondence to Dr. Atlee, B6/386 Clinical Science Center, 600 Highland Avenue, Madison, WI 53792.

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Table 1. The Effects of Thiopental on the Mean (± SEM) Dose of Epinephrine (μg/kg) Required for Initiation of Atrioventricular Dissociation (AVD) or Atrial and Ventricular Dysrhythmias in Group 1 Dogs

Anesthetic	SAP–WAP	AT ECT	AVD	V ECT	V BIG	V TACH
ENF	0.5 ± 0.1 (11)	2.2 ± 0.2 (7)	2.4 ± 0.8 (6)	7.5 ± 1.4 (10)	9.8 ± 1.6 (9)	12.2 ± 1.8 (8)
ENF–THIO	0.5 ± 0.0 (11)	2.1 ± 0.4 (8)	2.3 ± 0.4 (5)	3.3 ± 0.7 (11)[a]	3.5 ± 0.5 (9)[a]	5.3 ± 1.0 (11)[a]
ISO	0.7 ± 0.1 (11)	3.3 ± 0.9 (9)	1.8 ± 0.4 (7)	9.4 ± 2.9 (8)	0.8 (1)[b]	(0/11)[b]
ISO–THIO	0.8 ± 0.2 (11)	2.5 ± 0.5 (9)	2.8 ± 0.5 (8)	9.8 ± 2.5 (11)[b]	5.3 ± 3.0 (2)[b]	10.3 ± 2.7 (5)[a,b]

$n = 11$. Number of dogs with dysrhythmias is shown in parentheses.

Abbreviations: SAP–WAP, shift in or wandering atrial pacemaker; AT–ECT, atrial ectopy; V ECT, ventricular ectopy; V BIG, ventricular bigeminy; V TACH, ventricular tachycardia; ENF, enflurane only; ENF–THIO, enflurane after induction with thiopental; ISO, isoflurane only; ISO–THIO, isoflurane after induction with thiopental.

[a] $P \leq 0.05$ vs same anesthetic without THIO.

[b] $P \leq 0.05$ ISO vs ENF or ISO-THIO vs ENF-THIO.

maintain end-tidal CO_2 values (Beckman LB-2 analyzer) between 35 and 40 mm Hg. End-tidal anesthetic levels (Beckman LB-2 analyzer) equivalent to 1.25 MAC for enflurane (2.75%) and isoflurane (1.88%) were maintained (6). In addition, arterial blood gas tension and serum K^+ levels were measured before and after each epinephrine infusion. Sodium bicarbonate was administered between epinephrine infusions to correct base deficits greater than 3 mEq/L. Femoral arterial and airway pressures (Statham P23Db transducer), the surface electrocardiogram (Lead II), and catheter high right atrial and His bundle electrocardiograms were simultaneously displayed (Electronics for Medicine VR-12; Norland 3001 processing, digital oscilloscope) and recorded (Vetter FM recorder). Esophageal temperature ranged from 36.0 to 38.0°C. Saline (0.9 N) was administered (3–5 $ml \cdot kg^{-1} \cdot hr^{-1}$) into a forelimb vein.

Anesthetics and Epinephrine

Each dog was tested at weekly intervals under the following randomized test conditions: 1) enflurane alone, 2) enflurane after thiopental induction, 3) isoflurane alone, 4) isoflurane after thiopental induction. The desired end-tidal anesthetic level was maintained for 30 min prior to testing with epinephrine. Epinephrine was infused during a 1–4-hour testing period after induction. Epinephrine was infused centrally (external jugular or femoral vein) in graded doses between 0.5 and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. (The epinephrine dose was doubled until ventricular tachycardia appeared, and then determined to the nearest 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$—e.g., 0.5 to 1.0 to 2.0 to 4.0 to 8.0 to 6.0 to 5.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$.) Infusions were not begun until blood pressure, heart rate, and rhythm had returned to baseline after the previous infusion (10–40 min). Each infusion was continued until either ventricular tachycardia appeared or 2.5 min (group 1 dogs, see below) or 3.0 min (group 2 dogs, see below) had elapsed. The highest epinephrine infusion level used in any dog was 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, because in pilot experiments two dogs (enflurane–thiopental) had ventricular fibrillation at this level of epinephrine and could not be resuscitated. Additionally, the infusion of larger amounts of epinephrine would have been clinically irrelevant. Amounts of epinephrine in excess of 10 μg/kg are larger than those recommended for surgical hemostasis during halothane anesthesia (7), or those that appear safe with either enflurane or isoflurane (3).

Group 1 Dogs

Eleven dogs were tested in the same manner as previously used to determine the effect of thiopental induction on epinephrine dysrhythmias with halothane (2). Dysrhythmias were categorized as shift in or wandering atrial pacemaker, the appearance of atrioventricular (AV) dissociation associated with AV junctional or idioventricular beats or rhythm (rate < 120 beats/min), atrial ectopic beats, ventricular ectopic beats, ventricular bigeminy, and ventricular tachycardia (2). The dose (μg/kg) of epinephrine for each category of rhythm disturbance was calculated as the product of epinephrine infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$) and time (min) to dysrhythmia. Infusions lasted 2.5 min in group 1 dogs, the same as in our previous study with halothane and thiopental (2). Finally, eight of the 12 group 1 dogs were tested on two additional occasions (also randomized) to determine whether epinephrine doses for dysrhythmias with enflurane or isoflurane were the same 1–2 (EARLY) or 3–4 hr (LATE) after thiopental induction (2). Dogs were tested with the same levels of epinephrine (enflurane: 1.0, 2.0, and 4.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$; isoflurane: 1.0, 4.0, and 6.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) both EARLY and LATE after induction with thiopental.

Table 2. Mean (± SEM) Epinephrine Dose (μg/kg) Required for Production of AVD or Atrial and Ventricular Dysrhythmias with Enflurane and Isoflurane 1–2 hr (EARLY) and 3–4 hr (LATE) after Induction with Thiopental in Eight Group 1 Dogs

Time	SAP–WAP	AT ECT	AVD	V ECT	V BIG	V TACH
EARLY (enflurane)	1.1 ± 0.3	1.7 ± 0.7	1.2 ± 0.2	5.0 ± 1.7	3.8 ± 0.7	5.6 ± 0.7
LATE (enflurane)	0.7 ± 0.1	3.4 ± 0.8	2.4 ± 0.8	3.9 ± 1.0	4.0 ± 1.0	5.8 ± 1.0
n	8	2	3	7	7	6
EARLY (isoflurane)	0.7 ± 0.1	5.1 ± 1.5	2.7 ± 0.6	12.0 ± 3.8	0	12.4 ± 0
LATE (isoflurane)	0.6 ± 0.2	2.6 ± 1.1	4.4 ± 1.5	6.6 ± 2.4	0	11.6 ± 0
n	8	3	5	3	0	1

n, number of dogs in which these dysrhythmias occurred both EARLY and LATE.
Abbreviations are the same as in Table 1.

Group 2 Dogs

Another eight dogs were tested on weekly occasions (randomized) to determine the arrhythmic dose (ADE in μg/ml) and plasma level (PLE in ng/ml) of epinephrine at ventricular arrhythmias (four or more ventricular extrasystoles in 15 sec (5,8)) during enflurane, enflurane–thiopental, isoflurane, or isoflurane–thiopental. Methods were identical to those above, except for the following: Epinephrine was infused over 3.0 min and a bracketing method used to establish ADE. Beginning with 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, the epinephrine infusion level was doubled up to 8.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, unless the arrhythmias were encountered at 4.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. If there were arrhythmias at 8.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, 6.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was tested; if not, 10.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (highest level) was tested. No animal was tested with more than five epinephrine infusion levels; usually, only three or four were required to find the ADE. Plasma epinephrine levels were determined from an arterial blood sample withdrawn at the time the ADE was encountered. Arterial samples for PLE (below) were also collected at 1.0, 2.0, and 3.0 min with 1.0 and 2.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine (enflurane, enflurane–thiopental) and 2.0 and 4.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (isoflurane, isoflurane–thiopental). In addition, arterial blood was sampled at the end of the 10.0-$\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine infusion in dogs tested with isoflurane or isoflurane–thiopental who did not develop ventricular arrhythmias by 3.0 min.

Epinephrine Plasma Level Determinations

Blood samples for measurement of epinephrine plasma levels were withdrawn into precooled plastic tubes containing an EDTA-metabisulfite solution (supplied by Mayo Medical Laboratories, Rochester, Minnesota). These were centrifuged at 2°C for three minutes at 4000 rpm. Samples were then separated and stored at −20°C until sent within 7 days on dry ice to Mayo Medical Laboratories for analysis. High performance liquid chromatography (epinephrine sensitivity > 10 pg/ml) was used for analysis (9,10).

Data Analysis

The data were censored, because the highest epinephrine infusion level (10 $\mu g \cdot kg^{-1} \cdot min^{-1}$, lasting 2.5 or 3.0 min) provided a maximum epinephrine dose of 25 or 30 μg/kg. Thus a paired *t*-test could not be used for comparing the dose of epinephrine for dysrhythmias with enflurane and isoflurane, or these same anesthetics after thiopental induction. Instead, the Wilcoxon signed rank test was used (11). Student's *t*-test and graphic methods were used for all other comparisons.

Results

Arterial Blood Gas and Serum Potassium Values

Arterial blood gas tensions prior to testing in group 1 and 2 dogs were the following: pH 7.35–7.42, Pa_{CO_2} 33–42 torr, and $Pa_{O_2} > 350$ torr. Calculated base deficits were ≤ 3.0 mEq/L. Although there was an increase (0.3–2.9 mEq/L) in serum potassium (K^+) after epinephrine infusions, serum K^+ ranged from 3.4 to 4.6 mEq/L prior to testing with epinephrine.

Group 1 Dogs

Epinephrine doses for atrial dysrhythmias and AV dissociation with enflurane were not different from those with isoflurane, nor were they affected by thiopental with either agent (Table 1). Thiopental reduced the epinephrine dose for all types of ventricular rhythm disturbances with enflurane, but only for ventricular tachycardia with isoflurane (Table 1). Compared with enflurane or enflurane–thiopental, the epinephrine dose for ventricular bigeminy or tachycardia was greater ($P \leq 0.05$) with isoflurane or isoflurane–thiopental

Table 3. Increase in Systolic Blood Pressure (mm Hg; mean ± SEM) for Atrioventricular Dissociation or Ventricular Dysrhythmias Associated with the Infusion of Epinephrine During Anesthesia in 12 Group 1 Dogs

Anesthetic	AVD	V ECT	V BIG	V TACH
ENF	125 ± 30 (6)	172 ± 14 (10)	188 ± 12 (9)	198 ± 12 (8)
ENF–THIO	104 ± 16 (5)	159 ± 17 (11)	186 ± 14 (9)	176 ± 15 (11)
ISO	110 ± 8 (7)	177 ± 21 (8)	210 ± 90 (1)	(0)
ISO–THIO	87 ± 16 (8)	132 ± 19 (11)	182 ± 46 (2)	170 ± 14 (5)

Number of dogs with dysrhythmias is shown in parentheses.
Abbreviations same as in Table 1.

Table 4. Arrhythmic Dose of Epinephrine (ADE, μg/ml), Plasma Level of Epinephrine (PLE, ng/ml), Time (min) to Dysrhythmias (Four or More Ventricular Ectopic Beats within 15 sec), and Level of Epinephrine Infusion Associated with Onset of Dysrhythmias ($\mu\text{·kg}^{-1}\text{·min}^{-1}$) in Group 2 Dogs ($n = 8$).

Condition	*n*	ADE	PLE	Time	Level
ENF	8	9.1 ± 1.0	141 ± 24	1.8 ± 0.2	5.0 ± 0.5
ENF–THIO	8	5.0 ± 0.6^a	63 ± 16^a	1.9 ± 0.2	2.8 ± 0.3^a
ISO	1	28.3^b	330^b	2.8	10.0^b
ISO–THIO	5	15.2 ± 2.8^b	265 ± 59^b	2.1 ± 0.2	7.8 ± 1.2

Values shown are mean ± SEM.
n, number of dogs with dysrhythmias.
[a] $P < 0.05$ ENF–THIO vs ENF or ISO–THIO vs ISO.
[b] $P < 0.05$ ISO vs ENF or ENF–THIO vs ISO–THIO.
Abbreviations for anesthetics same as in Table 1.

(Table 1). The epinephrine dose for ventricular ectopy was not different from isoflurane compared with enflurane, but greater ($P < 0.05$) for isoflurane–thiopental compared with enflurane–thiopental (Table 1). Values for the epinephrine dose for various types of dysrhythmias 1–2 hr (EARLY) and 3–4 hr (LATE) after thiopental induction are shown for eight group 1 dogs in Table 2. There were no statistically significant differences for the dose of epinephrine for any type of dysrhythmia determined EARLY or LATE with either enflurane or isoflurane. Finally, values for the systolic blood pressure increase (before epinephrine vs at time of dysrhythmia) with epinephrine for AV dissociation and ventricular dysrhythmias are shown for 12 group 1 dogs in Table 3. There was no statistically significant difference in the increase in blood pressure with any category of dysrhythmia with enflurane compared with enflurane–thiopental, or isoflurane compared with isoflurane–thiopental. Nor was the increase in blood pressure with various types of dysrhythmias different for isoflurane or isoflurane–thiopental with enflurane or enflurane–thiopental (Table 3).

Group 2 Dogs

The arrhythmic dose (ADE) and PLE for ventricular dysrhythmias (four or more ventricular extrasystoles with 15 sec) in group 2 dogs is shown in Table 4. Also shown (Table 4) is the time during epinephrine infusion at which dysrhythmias occurred, as well as the epinephrine infusion level for dysrhythmias. Both ADEs and PLEs were greater ($P < 0.05$) with enflurane compared to enflurane–thiopental, and with isoflurane compared to enflurane. Thiopental did not significantly reduce the ADE ($P = 0.08$) or PLE ($P = 0.076$) with isoflurane in group 2 dogs (Table 4). Finally, plasma epinephrine levels reached at 1.0, 2.0, and 3.0 min during epinephrine infusions are shown for enflurane and for enflurane–thiopental at 1.0 $\mu\text{g·kg}^{-1}\text{·min}^{-1}$ (Fig. 1), isoflurane and isoflurane–thiopental at 4.0 $\mu\text{g·kg}^{-1}\text{·min}^{-1}$ (Fig. 2) and for all test conditions at 2.0 $\mu\text{g·kg}^{-1}\text{·min}^{-1}$ (Fig. 3). Irrespective of epinephrine infusion level or test condition, stable plasma epinephrine levels were reached by 2.0 min, the time at which the majority of dysrhythmias occurred (Table 4). Additionally, thiopental had no effect on epinephrine plasma levels reached with enflurane or isoflurane ($P < 0.05$). Finally, the epinephrine plasma level reached at 3.0 min after epinephrine, 10 $\mu\text{g·kg}^{-1}\text{·min}^{-1}$ in dogs without dysrhythmias, was 579 ± 64 ng/ml during isoflurane ($n = 6$ dogs), and 457 ± 125 ng/ml during isoflurane–thiopental ($n = 2$ dogs).

Discussion

These data indicate that induction of anesthesia with thiopental potentiates several types of epinephrine-induced ventricular rhythm disturbances in dogs

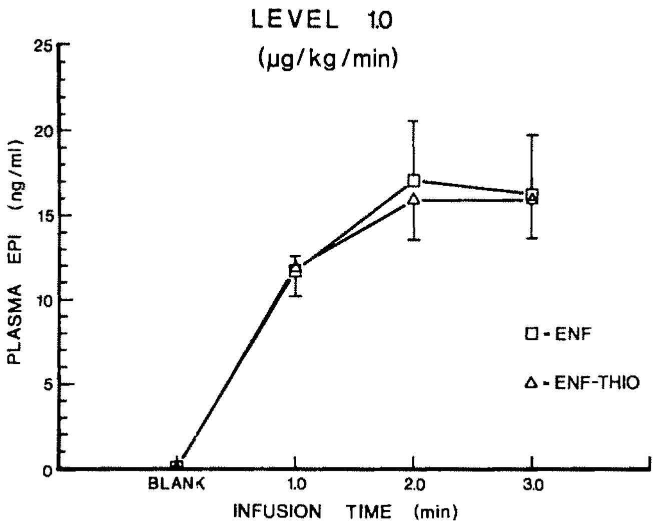

Figure 1. Plasma epinephrine (EPI) levels reached during the infusion of EPI (1.0 μg·kg^{-1}·min^{-1}) over 3.0 min in group 2 dogs (n = 8) anesthetized with enflurane (ENF) and enflurane–thiopental (ENF-THIO). The bars indicate SEM. Blank, plasma EPI level prior to EPI infusion.

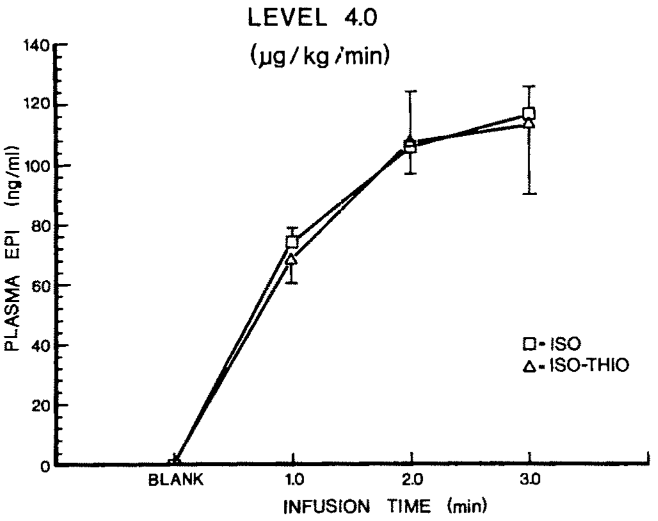

Figure 2. Plasma epinephrine (EPI) levels reached during the infusion of EPI (4.0 μg·kg^{-1}·min^{-1}) over 3.0 min in group 2 dogs (n = 7) anesthetized with isoflurane (ISO) or isoflurane–thiopental (ISO-THIO). Abbreviations, bars, and blank same as in Figure 1.

anesthetized with enflurane, but only ventricular tachycardia with isoflurane. Furthermore, potentiation by thiopental of epinephrine-induced ventricular dysrhythmias with enflurane lasts for up to four hours. Supraventricular dysrhythmias and AV dissociation (associated with AV junctional or ventricular escape beats or rhythm) were not potentiated by thiopental with either anesthetic. Both ADEs and PLEs associated with ventricular dysrhythmias were reduced when enflurane was preceded by thiopental, and with enflurane alone or enflurane plus thiopental compared with isoflurane or isoflurane plus thiopental. In contrast to a previous report of anesthetic effects on ADEs and PLEs (including that of enflurane after thiopental) in which a different dog was used for each experiment (5), in the present experiments the same dog was tested with each of four anesthetics (enflurane or isoflurane alone, and enflurane or isoflurane after thiopental). Plasma epinephrine levels reached with comparable levels of epinephrine infusion were similar for each anesthetic condition. Thus thiopental potentiation of sensitization, as well as increased sensitization with enflurane, do not appear related to an effect of thiopental or anesthetic (enflurane compared to isoflurane) on epinephrine metabolism. Our observation that thiopental potentiates sensitization with enflurane is similar to the effect of thiopental on epinephrine-induced dysrhythmias in dogs anesthetized with halothane (2). Indeed, the doses of epinephrine for various types of ventricular dysrhythmias with enflurane preceded by thiopental (Table 1) are nearly the same as those previously reported for halothane alone (ventricular ectopy, 3.8 ± 0.7; ventricular bigeminy, 4.0 ± 1.0; ventricular tachycardia, 5.5 ± 0.3 μg/ml) (2).

Our values for ADE and PLE with enflurane and thiopental (Table 4) are substantially lower than those obtained, also in dogs, by Sumikawa et al. (5). They found an ADE of 20.9 ± 3.5 μg/ml and PLE of 206.3 ± 17.9 ng/ml for the same level of enflurane preceded by thiopental induction (20 mg/kg). Their dysrhythmia end point and method of epinephrine assay (high performance liquid chromatography) were the same as those used in this study. However, their method for the infusion of epinephrine differed, which may explain the different results obtained in the two studies. In the study by Sumikawa, epinephrine was infused according to the method of Pace et al. (8), that is, over 3 min, beginning with a dose of 0.67 μg·kg^{-1}·min^{-1}, which was increased by $e^{0.2}$ (e = 2.72) amounts until the dysrhythmia (4 or more ventricular ectopic beats in 15 sec) occurred. Also, only 10 min elapsed between infusions (5,8), compared with 10–40 min in this study. We calculate that 13 successive infusions were required to reach the mean infusion rate (11.4 ± 1.4 μg·kg^{-1}·min^{-1}) at which ADE and PLE were obtained in Sumikawa's study (5). MacCannell and Dresel have shown (cyclopropane-anesthetized dogs) that repeated challenges with epinephrine lead to tolerance and the inability to produce dysrhythmias, or the requirement for much higher doses of epinephrine for dysrhythmias (12). Perhaps epinephrine tolerance could have led to the higher reported values for ADE and PLE with enflurane and

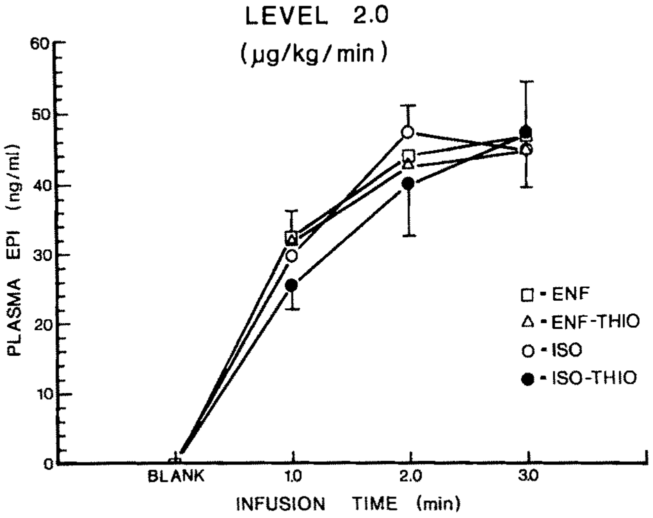

Figure 3. Plasma epinephrine (EPI) levels reached during the infusion of EPI (2.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$) over 3.0 min in group 2 dogs anesthetized with enflurane (ENF) or enflurane–thiopental (ENF-THIO), or isoflurane (ISO) or isoflurane–thiopental (ISO-THIO). Abbreviations, bars, and blank same as in Figure 1.

thiopental in the study of Sumikawa et al. (5). Tolerance to epinephrine could also explain the higher ADE for isoflurane alone (dogs, 23 ± 3 μg/kg) obtained by Joas and Stevens (4).

The mechanism for thiopental potentiation of several types of epinephrine-induced ventricular dysrhythmias with enflurane, and ventricular tachycardia with isoflurane, does not appear to involve altered metabolism of epinephrine in dogs pretreated with thiopental, or differences in epinephrine metabolism between enflurane and isoflurane, because plasma levels were similar for the same level of epinephrine infusion with or without thiopental. Admittedly, we did not compare higher epinephrine infusion levels with isoflurane. This was because most dogs with isoflurane and thiopental reached their ADE during the infusion of epinephrine at or below 8.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Similar values for epinephrine plasma level in group 2 dogs at the end of epinephrine, 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with isoflurane (6 dogs) and isoflurane–thiopental (2 dogs), suggest that thiopental also does not affect plasma epinephrine levels reached with higher epinephrine infusion levels. Nor does the thiopental effect on epinephrine-induced dysrhythmias appear related to increases in systolic blood pressure above baseline levels at the time of dysrhythmia (Table 3), as we have shown with halothane (2). Although the increase in systolic blood pressure with each category of dysrhythmia (Table 3) appears greater without thiopental pretreatment, possibly reflecting higher epinephrine infusion levels, this was not statistically significant. Nor were the differences in increases in systolic pressure with enflurane or isoflurane significant. Consequently, we propose the following as a mechanism for thiopental potentiation of epinephrine-anesthetic ventricular dysrhythmias.

It is known that thiopental (13) and halothane (14) (the effects of enflurane and isoflurane have not been reported) have contrasting effects on the action potential in ventricular muscle. Because the effects involve duration of action potential and refractoriness, we postulate an interaction between thiopental and the anesthetics that increases the temporal dispersion of refractoriness in ventricular muscle. Critical changes in refractoriness could favor reentrant ventricular dysrhythmias, one proposed mechanism for epinephrine-induced ventricular dysrhythmias with halothane (15). Alternatively, thiopental and halothane may be shown to have contrasting effects at sometime on abnormal mechanisms for automaticity in ventricular fibers; that is, spontaneous depolarization in fibers with a reduced level of membrane potential. Such mechanisms may be initiated by exposure to catecholamines and high extracellular potassium (16).

Our data were obtained in dogs and therefore might not apply to humans, although the dog is a widely used model for the human condition. Johnston et al. found an ED_{50} (positive ventricular dysrhythmia response in 50% of patients) of 10.9 μg/kg for enflurane, and 6.7 μg/kg for isoflurane, in patients undergoing transphenoidal removal of pituitary tumors who received submucosal injections of epinephrine (3). Their dysrhythmia end point differed from ours: it was three ventricular extrasystoles at any time during or immediately after (3–10 min) epinephrine injections. Also, submucosal epinephrine injection, with the possibility of variable rates of absorption, is not the same as central intravenous injection. Despite these limitations, the ED_{50} values obtained by Johnston et al. (3) are not too different for enflurane and isoflurane from those found for ventricular ectopy in our Group 1 dogs. However, the study by Johnston et al. (3) could be somewhat misleading because there were too few patients anesthetized with enflurane that had positive dysrhythmia responses to determine an ED_{50} for enflurane.

Our finding of thiopental potentiation of epinephrine-induced ventricular dysrhythmias with enflurane may have clinical relevance. The first author has observed what may have been multiform ventricular premature beats (interpreted as multifocal atrial tachycardia with aberrant ventricular conduction) in a patient anesthetized with thiopental–enflurane–oxygen, who received a total of 30 μg of epinephrine

(6.0 ml 1:200,000 epinephrine in 0.5% lidocaine) injected submucosally (17).

In conclusion, our findings in dogs confirm the clinical impression that enflurane and isoflurane are less sensitizing than halothane. They suggest that, as with halothane (2), induction of anesthesia with thiopental may increase the likelihood of catecholamine-mediated ventricular dysrhythmias. However, this would require a dose of epinephrine far exceeding that recommended for surgical hemostasis with halothane (recommended dose, 1.0 $\mu g \cdot kg^{-1} \cdot 10\ min^{-1}$) (3,7). We hasten to add that a "safe" dose has not been established in humans for epinephrine with either enflurane or isoflurane. Plasma levels of epinephrine equivalent to those measured in this study have been observed in patients with pheochromocytoma, particularly during surgical manipulation of the tumor (18). Thus it might be prudent to avoid induction with thiopental in patients with pheochromocytoma when enflurane or isoflurane are to be used for anesthesia. Also, as with halothane (2), and if our present findings are applicable to humans, epinephrine-induced ventricular dysrhythmias often may be preceded—that is, at a lesser dose or plasma level of epinephrine—by atrial dysrhythmias and AV junctional or ventricular escape beats or rhythm associated with AV dissociation. Hence, these lesser rhythm disturbances can be viewed as harbingers for more serious dysrhythmias. Finally, the problem of catecholamine-mediated dysrhythmias is still an important clinical issue—for example, stress-mediated catecholamine release, vasopressors, bronchodilators, and autonomic imbalance, in addition to causes mentioned above. Thus it is likely that anesthesiologists will continue to search for less sensitizing anesthetic agents and techniques. If so, our results also suggest that serious consideration should be given to possible modifying effects of other drugs or procedures used to test for sensitization.

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ANESTH ANALG
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Cardiovascular Toxicity of Local Anesthetics:
An Alternative Hypothesis

Richard D. Thomas, BS, Michael M. Behbehani, PhD, Dennis E. Coyle, PhD, and Donald D. Denson, PhD

THOMAS RD, BEHBEHANI MM, COYLE DE, DENSON DD. Cardiovascular toxicity of local anesthetics: an alternative hypothesis. 1986;65:444–50.

The current study examined the possibility that high local anesthetic concentrations within the central nervous system could contribute to the toxic cardiovascular effects observed clinically after an accidental intravenous injection. Equal numbers of molecules of lidocaine (1.6 μl of a 2% solution) and bupivacaine (1.0 μl of a 4% solution) were injected at three vasomotor and cardioactive areas in the rat medulla by means of a 28-gauge hypodermic needle and a microsyringe. These areas were the C1 region, the intermediolateral column (IML), and the nucleus tractus solitarius (NTS). Both lidocaine and bupivacaine at C1 significantly decreased mean arterial pressure and, at IML, resulted in significant bradycardia and hypotension. At NTS, both lidocaine and bupivacaine caused significant bradycardia and hypotension, which were accompanied by ventricular arrhythmias in 55% of the animals. In all animals in whom ventricular arrhythmias were associated with lidocaine, the arrhythmias spontaneously reverted to normal sinus rhythm. In 50% of animals developing ventricular arrhythmias after bupivacaine, the arrhythmias resulted in death. Using an equal number of molecules of lidocaine and bupivacaine, all three regions studied demonstrated that bupivacaine was 2–4 times more potent than lidocaine in producing cardiovascular effects. These data demonstrate that direct application of local anesthetics within the medullary region of the central nervous system can result in hypotension, bradycardia, and ventricular arrhythmias similar to what may be seen in humans after accidental intravenous injections of local anesthetics. Moreover, the sites and mechanisms of action appear to be identical for bupivacaine and lidocaine. Thus bupivacaine does not appear to be an aberrant local anesthetic, as some have suggested, but rather produces more profound effects related to its potency and physicochemical properties.

Key Words: ANESTHETICS, LOCAL—lidocaine, bupivacaine. TOXICITY—local anesthetic.

Numerous in vivo and in vitro studies have examined the etiology of reported cardiotoxicity of bupivacaine (1–8). Most recently, Clarkson and Hondeghem reported that in guinea pig ventricular muscle, both lidocaine and bupivacaine produce direct myocardial depression by blocking cardiac sodium channels (8). Bupivacaine was found to be a more potent channel blocker, which was attributed to differences in binding affinity and sodium channel association kinetics. The in vitro studies of Clarkson and Hondeghem produced signs of cardiovascular toxicity similar to those reported in vivo in sheep (3,5). Other mechanisms proposed for cardiotoxicity focus on the ability of bupivacaine to depress atrioventricular (AV) node conduction and/or myocardial contractility (4–7). However, none of the studies to date has considered the possibility of concomitant cardiovascular system (CVS) and central nervous system (CNS) toxicity, which have been reported under clinical circumstances in humans (9). These clinical observations have led to the suggestion that toxicity associated with bupivacaine is different from the toxicity ascribed to other amide local anesthetics. Whereas isolated heart experiments allow evaluation of direct myocardial effects, in vivo studies involving systemic administration do not allow independent observations of the specific isolation into the discrete contributions of the CNS and CVS to the observed toxicity. A central mechanism for the inotropic and chronotropic actions of lidocaine has been reported (10). A marked increase in the brain–blood partitioning during convulsions has also been reported for lidocaine, suggesting an increased permeability of local anesthetics across the

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Address correspondence to Dr. Denson, Department of Anesthesia, University of Cincinnati College of Medicine, Cincinnati, OH 45267–0531.

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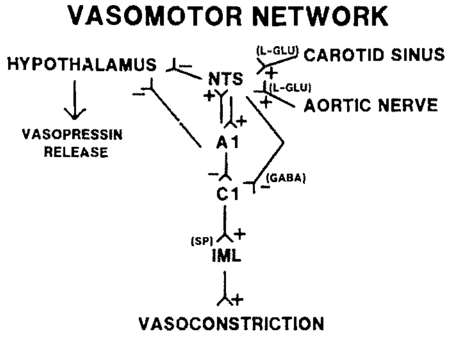

Figure 1. Schematic diagram of the vasomotor and cardioactive areas of the medulla. Nucleus tractus solitarius produces an inhibitory (—< −) influence on the C1 cell bodies. The C1 cell bodies in turn produce an excitatory influence (—< +) on the intermediolateral column resulting in vasoconstriction.

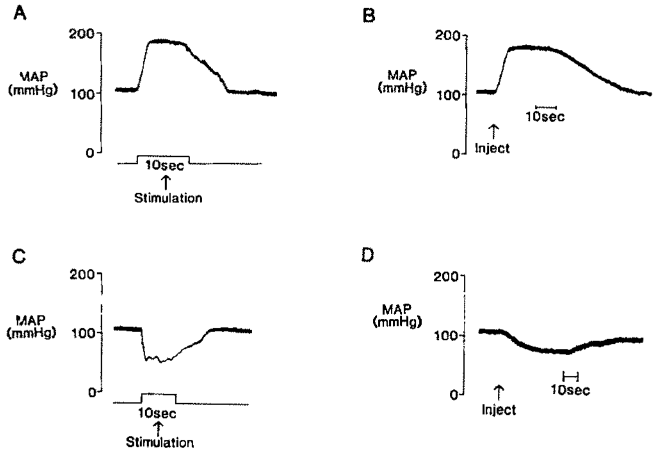

Figure 2. The effect of electrical and chemical stimulation at C1 and NTS on mean arterial pressure. (A) Response of blood pressure to electrical stimulation of C1 cell bodies. (B) Response of blood pressure to chemical stimulation of C1 cell bodies. (C) Response of blood pressure to electrical stimulation of NTS. (D) Response of blood pressure to chemical stimulation of NTS.

blood–brain barrier during local anesthetic-induced seizures (11). Because the CNS can exert dromotropic, inotropic, and chronotropic effects on the myocardium, some of the cardiovascular system depressant effects of amino-amide local anesthetics might possibly be mediated through CNS mechanism(s) (12). If this hypothesis were true, then the apparently simultaneous onset of CNS and CVS toxicity with bupivacaine could be explained in part by extremely high brain concentrations. This study was designed to evaluate the potential contribution of the CNS to cardiac toxicity associated with amide local anesthetics by use of an in vivo model that obviates the need for systemic administration of the anesthetics.

Methods

General Procedure

Adult Sprague-Dawley rats (Charles River Laboratories) weighing 200–300 g were anesthetized with chloral hydrate (400 mg/kg). The femoral artery was cannulated for a continuous recording of blood pressure, using a blood pressure monitor 813B (CSP Inc.) and a Gould Brush 260 recorder. The animals were placed in a sterotactic instrument in the prone position. The dorsal surface of the skull was exposed, and the occipital bone was either partially or entirely excised. Figure 1 is a schematic of the primary vasomotor and cardioactive areas of the medulla. The nucleus tractus solitarius (NTS) is a primary relay station for sympathetic and parasympathetic afferent and efferent fibers of the cardiovascular system. Fibers from NTS have an inhibitory effect on the hypothalmus and on C1 cell bodies. The nucleus tractus solitarius receives excitatory signals from fibers of the carotid sinus and aortic nerve. C1 cell bodies receive inhibitory input from NTS and A1 cell bodies. Fibers from C1 cell bodies send excitatory signals to the intermediolateral column (IML) located in the cervical spinal cord (12,13). For experiments in the C1 area and the NTS an area of the occipital bone 3.0 mm wide and 2.0 mm long was excised. For injections at the IML (cervical spinal cord), the entire occipital bone was excised. Lead I electrocardiogram was continuously recorded using a Gould Brush 260 recorder.

Injections of saline caused no changes in mean arterial pressure, heart rate, PR interval, or QRS duration when injected at C1, the IML, or the NTS. In addition to positive response to chemical and electrical stimulation of correct electrode and cannula placement, anatomical verification of electrode and cannula location was required before animals were included in their experimental group. A minimum of seven animals meeting these criteria was included in each set of experiments.

The effects of local anesthetics on the fibers of the NTS and C1 (effects on cell firing rate) were studied first using bupivacaine as a model compound. A comparison between equal numbers of molecules of lidocaine and bupivacaine was then completed by injections at the NTS, C1, and the IML.

Location of C1 and the NTS

The stereotactic coordinates of C1 were 12.2–13.0 mm caudal with respect to the bregma, 0.7–1.0 mm lateral from the midline, and 7.5–8.5 mm deep with respect to the brain surface. The nucleus tractus solitarius was

Table 1. Cardiovascular Effects of Bupivacaine and Lidocaine Injected at C1[a]

	Mean arterial pressure (mm Hg)	Heart rate (beats/min)	PR interval (msec)	QRS duration (msec)
Bupivacaine (4%, 1.4 μM)	−36.6 ± 7.4[b]	−6.7 ± 6.3	9.7 ± 8.4	−1.7 ± 0.8
Lidocaine (2%, 1.4 μM)	−21.6 ± 1.8[b]	−26.4 ± 20.3	0.0 ± 0.0	0.0 ± 0.0

[a] Mean change from control ± SD.
[b] $P < 0.001$.

located at 12.8–13.5 mm caudal, 1.0–1.5 mm lateral, and 5.5–6.5 mm deep. The C1 and NTS areas were located by stimulation with bipolar pulses, 10 V and 400 μsec, at a frequency of 10 Hz for 10 sec using a Pulsar 4bp stimulator (Frederick Haer and Co.). To confirm that only nerve cell bodies and not fibers of passage were being stimulated, L-glutamate (50 mM in 0.9% NaCl, pH 6.9) was injected into the same area. For both electrical and L-glutamate stimulations, an increase of a minimum of 10 mm Hg in mean arterial pressure indicated correct location of C1, while a decrease of at least 10 mm Hg in mean arterial pressure indicated correct location of the NTS (Fig. 2). At the conclusion of the experiment, 0.6 μl of pontamine skyblue were injected through the cannula at either the C1 area or the NTS. After a midline thoracotomy, animals were perfused with 10% formalin via the aorta. Brains were then dissected to verify electrode and/or cannula placement.

Experiments at C1

After proper cannula and electrode placement in the C1 area, either an equal number of molecules of 4% bupivacaine (1 μl, 1.4μmol), or 2% lidocaine (1.6 μl, 1.4 μmol) or else 1 μl of saline was injected using a stainless steel 28-gauge hypodermic needle with a microsyringe. The effects of 4% bupivacaine (1 μl, 1.4 μmol) on the C1 cell firing rate in cells from 20 animals were measured using a 1 mm glass electrode filled with 3 M NaCl (window discriminator WDR-420, Syntronics Inc.) Arterial pressures and electrocardiogram were continuously monitored throughout these experiments.

Experiments at IML

After exposure of the cervical spinal cord, the dura mater was excised. A 28-gauge hypodermic needle was then placed 1 mm into the spinal cord between cervical vertebrae 1 and 2 and either 0.9% saline (1 μl), 4% bupivacaine (1 μl, 1.4 μmol), or 4% lidocaine (0.8 μl, 1.4 μmol) was infused into the cord. The arterial pressure and electrocardiogram were continuously monitored.

Experiments at the NTS

Experiments at the NTS involved placement of a stainless steel 28 gauge hypodermic needle connected to a microsyringe. Four percent bupivacaine (1 μl, 1.4 μmol), 2% bupivacaine (1 μl, 0.7 μmol), 2% lidocaine (1.6 μl, 1.4 μM), or 4% lidocaine (0.8 μl, 1.4 μmol), or 1 μl normal saline was infused into the NTS. Effects of 4% bupivacaine (1 μl, 1.4 μmol) on the NTS cell firing rate in cells from 20 animals were measured using a 1-mm glass electrode filled with 3M NaCl (window discriminator WDR-420, Syntronics Inc.) Arterial pressures and electrocardiogram were again continuously monitored throughout these experiments.

Statistical Analysis of the Data

Within-animal differences in mean arterial pressure, heart rate, PR interval, and QRS duration (taken as maximum changes from control) were compared using a *t*-test for paired data. Intergroup comparisons were made using a one-way analysis of variance followed by the appropriate critical value test for multiple comparisons. Data are presented as means ± SD. A value of $P < 0.05$ was considered the minimum level of statistical significance.

Results

Experiments at C1

The activity of C1 cells in 20 animals was recorded during the application of bupivacaine (1.4 μmol). Bupivacaine increased the cell firing rate from 23.7 ± 10.5 to 45.0 ± 7.2 Hz ($P < 0.01$). The cell firing rates returned to control values 20 min after injection.

Application of an equal number of molecules of either bupivacaine (1.4 μmol) or lidocaine (1.4 μmol) resulted in significant decreases in mean arterial pressure (Table 1). All hemodynamic changes began within 30 sec of injection. Maximum changes occurred at 2–5 min and lasted 10–15 min after injection. Hemodynamic parameters had returned to control values by 20 min after injection. Changes in heart rate, PR interval, and QRS duration were not statistically significant.

Table 2. Cardiovascular Effects of Bupivacaine and Lidocaine Injected at the IML[a]

	Mean arterial pressure (mm Hg)	Heart rate (beats/min)	PR interval (msec)	QRS duration (msec)
Bupivacaine (4%, 1.4 μmol)	−43.4 ± 10.0[b]	−50.3 ± 13.8[b]	1.7 ± 1.7	1.1 ± 1.0
Lidocaine (4%, 1.4 μmol)	−13.9 ± 5.0[c]	−25.5 ± 7.7[d]	−0.5 ± 1.2	1.5 ± 3.2

[a] Mean change from control ± SD.
[b] $P < 0.01$.
[c] $P < 0.05$.
[d] $P < 0.025$.

Table 3. Cardiovascular Effects of Bupivacaine and Lidocaine Injected at the NTS[a]

	Mean arterial pressure (mm Hg)	Heart rate (beats/min)	PR interval (msec)	QRS duration (msec)
Bupivacaine (2%, 0.7 μmol)	−27.1 ± 8.6[b]	−50.6 ± 22.0[c]	11.6 ± 5.6	4.5 ± 3.4
Bupivacaine (4%, 1.4 μmol)	−25.6 ± 6.8[b]	−85.1 ± 48.0[c]	5.6 ± 4.2	16.7 ± 8.0
Lidocaine (2%, 1.4 μmol)	−12.5 ± 5.7[c]	−37.9 ± 19.3[c]	9.2 ± 6.2	2.0 ± 1.9
Lidocaine (4%, 1.4 μmol)	−8.0 ± 3.1[b]	−3.2 ± 7.8	1.09 ± 2.04	5.8 ± 3.2

[a] Mean change from control ± SD.
[b] $P < 0.025$.
[c] $P < 0.05$.

Experiments at the IML

Application of an equal number of molecules of either bupivacaine or lidocaine (1.4 μmol) significantly decreased both mean arterial pressure and heart rate (Table 2). All hemodynamic changes began within 30 sec of injection. Maximum changes occurred at 2–5 min and lasted 10–15 min after injection. Hemodynamic parameters had returned to control values by 20 min after injection. No statistically significant electrocardiographic changes were noted for either bupivacaine or lidocaine.

Experiments at the NTS

The activity of NTS cells in 20 animals was recorded during the application of bupivacaine (1.4 μmol). Bupivacaine caused a decrease in the cell firing rate from 38.1 ± 10.6 to 17.6 ± 7.7 Hz ($P < 0.01$). The cell firing rates returned to control values within 20 min. Application of 1.4 μM of bupivacaine produced significant decreases in both mean arterial pressure and heart rate (Table 3). All hemodynamic changes began within 30 sec of injection. Maximum changes noted at 2–5 min lasted for 10–15 minutes after injection. Hemodynamic parameters had returned to control values within 20 min after injection. Electrocardiographic changes were noted within the first 5 min after injection. However, arrhythmias developed and worsened 15–20 min after injection. Prolongation of the PR interval and QRS duration were noted in many animals, but the increases were not statistically significant. Injection of 0.7 μM of bupivacaine in a volume identical to the previous experiments with 1.4 μmol of bupivacaine produced identical changes. Injection of 2% lidocaine (1.4 μmol) resulted in changes in mean arterial pressure, heart rate, PR interval, and QRS duration statistically similar to those described for both bupivacaine treatments, although the magnitude of the effects tended to be less severe. Injection of 1.4 μmol of lidocaine in one-half the volume, as described in the first series of lidocaine experiments, decreased mean arterial pressure, heart rate, and increases in PR interval and QRS duration. However, in this series, only the decrease in mean arterial pressure was statistically significant.

Ventricular Arrhythmias with Local Anesthetics Applied at C1, the IML, and the NTS

Application of an equal number of molecules (1.4 μmol) of either bupivacaine or lidocaine at the C1 area of the medulla resulted in no ventricular arrhythmias. Application of an equal number of molecules (1.4 μmol) of either bupivacaine or lidocaine at the IML was associated with ventricular arrhythmias in 14.3% of the animals in each group. Application of both 4% bupivacaine and 4% lidocaine in equimolar amounts (1.4 μmol) at the NTS produced ventricular arrhythmias in 55% of the animals in each group. When 2% bupivacaine (0.7 μmol) was applied to the NTS, ventricular arrhythmias occurred on 38% of the animals. When 2% lidocaine (1.4 μmol) was applied to the NTS, 36% of the animals developed ventricular arrhythmias. Figure 2 *A* and *B* chronologically sum-

Table 4. Frequency of Ventricular Arrhythmias Produced by Injection of Bupivacaine or Lidocaine at C1, the IML, or the NTS[a]

Area	Bupivacaine (2%, 0.7 μmol)	Bupivacaine (4%, 1.4 μmol)	Lidocaine (2%, 1.4 μmol)	Lidocaine (4%, 1.4 μmol)
C1	—	0/8	0/8	—
IML	—	1/7	—	1/7
NTS	3/8	6/11	4/11	6/11

[a] Frequency; minimum $n = 7$.

marizes the development of ventricular arrhythmias with 4% bupivacaine (1.4 μmol) and 2% lidocaine (1.4 μmol) placed at the NTS. In all animals in which 2% lidocaine, 4% lidocaine, and 2% bupivacaine were used, normal sinus rhythm returned within 30 min without treatment. When 4% bupivacaine was used, 50% of the animals developing ventricular arrhythmias returned to normal sinus rhythm within 30 min without treatment, whereas the ventricular arrhythmias were fatal in the other 50%.

In all cases, the onset of ventricular arrhythmias occurred between 5 and 15 min after application of either lidocaine or bupivacaine and reached maximum severity at 15 min. The frequency of occurrence of ventricular arrhythmias after injection of bupivacaine or lidocaine at C1, the IML, and the NTS are presented in Table 4.

Discussion

Chloral hydrate was selected as the anesthetic agent used in this study because it produces fewer alterations in normal CNS function than other commonly used anesthetics (14). The seemingly large amounts of bupivacaine and lidocaine used in the present study represent approximately 20% of the total amount expected in the brain of a rat under conditions producing cardiovascular system toxicity. This value was estimated using the blood–brain partitioning coefficient of 4.5 reported for lidocaine (11), a brain volume of 1.2 ml for a 250-g Sprague Dawley rat (15), and an end-injection arterial blood concentration of 70 μg/ml (Denson et al., unpublished results). These amounts were chosen for a maximum likelihood that slow diffusion in the presence of rapid systemic absorption would still allow blockage of enough fibers so that dromotropic, inotropic, and/or chronotropic effects could be detected. Two and four percent solutions were chosen so that the selected amounts of drug could be introduced in a volume small enough to maximize the exposure of only the desired region.

Results obtained in the C1 area suggest that the major action of both lidocaine and bupivacaine is on axons of the nerve cells rather than on cell bodies. If the drugs acted primarily on the C1 cell bodies, then application of local anesthetic to this region would have resulted in a decrease rather than an increase in cell firing rate. The observed increase in cell firing rate is consistent with the fact that all input to the C1 cell bodies is inhibitory in the resting state (Fig. 1). Thus blockade of these fibers would remove the inhibitory input, resulting in an increase in cell firing rate. The return of cell firing rate to control by 20 min after injection is consistent with the return of blood pressure to control values at 20 min after injection. The observation of hypotension without bradycardia or ventricular arrhythmias supports the hypothesis that in the resting state, the C1 region has a tonic excitatory influence on the spinal cord neurons that are involved in maintenance of arterial blood pressure. A comparison of equal numbers of bupivacaine and lidocaine molecules demonstrated that bupivacaine produced a more pronounced decrease in mean arterial pressure.

This hypothesis is further substantiated by the experiments at the IML, which resulted in the same decrease in mean arterial pressure as did similar experiments at C1. However, decreases in mean arterial pressure when either bupivacaine or lidocaine were applied at the IML were accompanied by significant decreases in heart rate. These results are in good agreement with clinical observations regarding high spinal anesthesia and again show a discrimination between bupivacaine and lidocaine, bupivacaine causing a more profound effect on both mean arterial pressure and heart rate.

Injections at the NTS produced several changes. The primary action of both bupivacaine and lidocaine at the NTS also appears to be on fibers rather than on cell bodies. This hypothesis is supported by the fact that local anesthetics resulted in a significant decrease in cell firing rate when applied to the NTS. The nucleus tractus solitarius receives only excitatory input fibers, and thus blockade of these fibers would be expected to result in a decrease in cell firing rate (Fig. 1). In addition to significant changes in blood pressure and heart rate, prolongation of the PR interval and QRS duration was observed in most animals. Bupivacaine appeared to be at least twice as potent as lidocaine in producing these changes. The nucleus tractus solitarius appears to be the most sensitive area of the three studied, in terms of chronotropic and dromotropic effects on the heart.

At each region, adverse effects on heart rate and blood pressure were noted almost immediately. However, maximum electrocardiographic effects were noted at 15 min. Diffusion coefficients calculated for bupivacaine and lidocaine are similar and suggest that 16

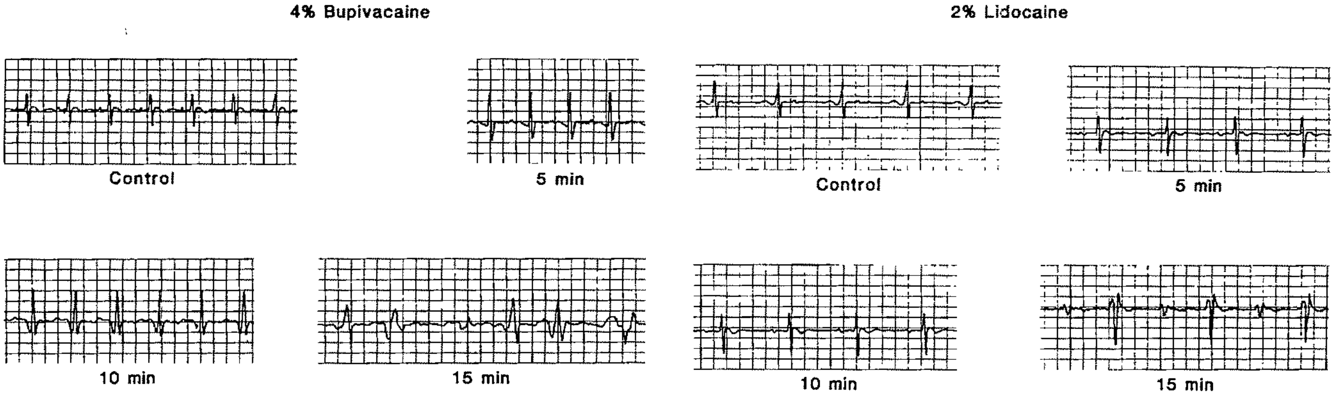

Figure 3. (A) Chronologic sequence of the development of ventricular arrhythmias following placement of 1.4 μmol of bupivacaine at NTS. (B) Chronologic sequence of the development of ventricular arrhythmias following placement of 1.4 μmol of lidocaine at NTS.

min are required for either drug to diffuse 1 mm^3 in biologic tissue. The time delay in arrhythmia development may be due to slow diffusion, with subsequent block of enough fibers to produce observable changes. Such a delay would not be expected after systemic administration because a uniform delivery of drug to these regions would be achieved by cerebral capillary blood flow.

The incidence of ventricular arrhythmias was similar when either bupivacaine or lidocaine were applied to the IML. Both local anesthetics produced arrhythmias with the same frequency when applied to the NTS. Although the incidence of ventricular arrhythmias was similar for both lidocaine and bupivacaine, it is important to understand that the qualitative aspects of the arrhythmias were very different for lidocaine and bupivacaine (Fig. 3). This difference is clearly illustrated by the fact that all lidocaine-induced arrhythmias spontaneously resolved, whereas 50% of the arrhythmias produced by bupivacaine proved fatal. No arrhythmias were recorded when either drug was applied in the C1 region. A combination of hypotension and bradycardia might possibly precipitate the ventricular arrhythmias noted in the present study. However, the time course of hypotension and bradycardia do not support this hypothesis because heart rate and to a greater extent blood pressure have nearly returned to control values by 15 min. These data suggest that local anesthetics have a direct dromotropic effect, particularly when placed at the NTS.

The observation that all animals that developed ventricular arrhythmias after lidocaine application reverted spontaneously to normal sinus rhythm whereas approximately 50% of the bupivacaine group did not, suggests that the "fast on–slow off" mechanism proposed by Clarkson and Hondeghem to explain differences in direct myocardial depressant effects of lidocaine and bupivacaine may also be operative within the CNS (8). In addition, lidocaine (and perhaps bupivacaine) may exhibit differential effects depending on the dose. Clearly, dose–response data are required to fully understand the present results.

Now that we have verified our hypothesis that chronotropic and dromotropic (and perhaps inotropic) changes can be produced by high concentrations of both bupivacaine and lidocaine in various medullary regions, the following question arises; can such effects occur in clinical practice? Simon et al. recently reported that uptake of lidocaine into the brain from blood increased by a factor of four during a convulsion (11). However, the original hypothesis of Simon et al. that the decreases in pH associated with convulsions resulted in increased uptake and increased intracellular "trapping" of lidocaine, has been refuted by Pardridge et al., who demonstrated a decrease in uptake of lidocaine by the brain with decreases in pH (16). These observations suggest there are alterations in the permeability of the blood–brain barrier resulting in increased drug extraction during convulsions. Other studies by Pardridge et al. demonstrated that lidocaine transport across the blood–brain barrier is independent of a α_1-acid glycoprotein concentration (17). Thus lidocaine does not obey the free drug hypothesis, which states that only free (unbound) drug is available for transport across the blood–brain barrier. Because α_1-acid glycoprotein is the predominant plasma protein for binding both lidocaine and bupivacaine at concentrations <10 μg/ml, we are conducting similar studies designed to elucidate the characteristics of movement of bupivacaine across the blood–brain barrier (18). The above observations suggest that abnormally high brain concentrations could accompany convulsions produced by local anesthetics resulting in adverse cardiovascular system effects.

The observations in the present study, which show the same incidence of arrhythmias with bupivacaine and lidocaine, could differ from clinical observations because the antiarrhythmic effect of lidocaine may counteract the CNS arrhythmic effect when lidocaine is given systemically. In the clinical setting, the magnitude of the CNS effects on the cardiovascular system will be governed by the physicochemical properties of the drug in question that dictate uptake of drugs into the CNS entry and accumulation. Accumulation of high concentrations of bupivacaine in the brain during convulsions could explain the apparently simultaneous onset of CNS and CVS toxicity. Moreover, the site(s) and mechanism(s) of action within the CNS appear to be identical for bupivacaine and lidocaine. Thus bupivacaine does not appear to be an "aberrant" local anesthetic structure as some have suggested, but rather produces more profound effects related to potency and physicochemical properties.

In conclusion, our data demonstrate direct application of local anesthetics within the medullary regions of the CNS can result in hypotension, bradycardia, and ventricular arrhythmias similar to those reported in humans after accidental intravenous injections of both bupivacaine and lidocaine (9,19). The fact that profound cardiovascular toxicity is observed clinically with bupivacaine but rarely with lidocaine argues that differences in physicochemical properties and blood–brain barrier transport characteristics do not allow sufficiently high concentrations of lidocaine to enter the cardioactive areas of the CNS. These data strongly suggest that CNS plays a role in mediation of the CVS toxicity of local anesthetics and demonstrate the need to consider both central nervous system and direct myocardial depressant properties when evaluating local anesthetic toxicity.

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Esmolol Attenuates Hemodynamic Responses during Fentanyl–Pancuronium Anesthesia for Aortocoronary Bypass Surgery

Lars R. Newsome, MD, Jonathan V. Roth, MD, Carl C. Hug Jr, MD, PhD, and David Nagle, MMSc

NEWSOME LR, ROTH JV, HUG CC Jr, NAGLE D. Esmolol attenuates hemodynamic responses during fentanyl–pancuronium anesthesia for aortocoronary bypass surgery. Anesth Analg 1986:65;451–6.

We evaluated the effects of esmolol, a short acting ($t_{1/2}\ \beta$ = 9 min) β-blocker on hemodynamics during noxious stimulation associated with aortocoronary bypass surgery. Group E (n = 10) and P (n = 10) patients had their morning dose of β- or calcium blockers withheld except for nifedipine, and were given infusions of esmolol (E) or placebo (P) beginning prior to anesthetic induction and continuing until mediastinal dissection. Group S (n = 10) patients received their usual medication the morning of surgery and received neither esmolol nor placebo. All patients received fentanyl infusions for anesthesia and pancuronium for relaxation. Esmolol patients had no changes in heart rate throughout the study. In contrast, significant increases in heart rate occurred during induction, intubation, and surgical stimulation in Groups P and S. Esmolol patients had a statistically significant but transient increase in pulmonary capillary wedge pressure (PCWP) after intubation, which did not require treatment. There were no significant changes in PCWP in Group S and a decrease in PCWP in Group P patients. We conclude that esmolol was effective in attenuating potentially deleterious responses to noxious stimulation during fentanyl–pancuronium anesthesia.

Key Words: ANESTHESIA, CARDIOVASCULAR. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—esmolol.

Fentanyl–oxygen–relaxant anesthesia is widely used for patients undergoing cardiac surgery. However, cardiovascular responses to noxious stimulation (tracheal intubation, skin incision, sternotomy) may occur in patients with good left ventricular function undergoing aortocoronary bypass surgery under fentanyl–pancuronium anesthesia (1). Such increases in myocardial O_2 demand may place these patients at increased risk for the development of myocardial ischemia. Perioperative myocardial ischemia appears to be an independent risk factor in the development of postoperative myocardial infarction (2). β-Adrenergic receptor antagonists have been used successfully to attenuate the sympathomimetic responses to anesthetic induction and tracheal intubation (3). Unfortunately, currently available β-adrenergic receptor antagonists have a long duration of action, which limits their flexibility in terms of terminating β-blockade if side effects should occur (4).

Esmolol is a new ultra-short-acting ($t_{1/2}\ \beta$ = 9 min) cardioselective β-adrenergic receptor antagonist (5). Esmolol has been shown to attenuate sympathomimetic responses to intubation in patients anesthetized with diazepam–N_2O–pancuronium, with ketamine, or with sodium thiopental (6–8). The purpose of this study was to determine whether esmolol can safely attenuate the cardiovascular responses to anesthetic induction, tracheal intubation, and surgical stimulation in patients anesthetized with fentanyl and undergoing elective aortocoronary bypass surgery.

Methods

After giving informed consent to the institutionally approved protocol, 30 patients with good left ventricular function (ejection fraction ≥ 0.45) undergoing elective aortocoronary bypass surgery were evaluated. Exclusion criteria included recent myocardial infarction (within 1 month of surgery), digoxin therapy,

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Address correspondence to Dr. Newsome, Department of Anesthesiology, Emory University Hospital, 1364 Clifton Road NE, Atlanta, GA 30322.

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or a history of asthma. Twenty patients were randomized to receive infusions of either esmolol (Group E) or placebo (Group P). This part of the study was double-blinded. In these 20 patients, β-adrenergic receptor and calcium entry blockers were withheld the morning of surgery, with the exception of nifedipine: nifedipine was given because it has less negative chronotropic effect than verapamil or diltiazem and there was concern by our Human Investigations Committee about withdrawing a drug used to treat coronary artery spasm. A standard therapy group (Group S), consisting of ten additional patients, were given their usual morning doses of β- and/or calcium channel blockers and received neither esmolol nor placebo. All three groups of patients were studied within a 4-month period. Premedication consisted of lorezepam, 0.05 mg/kg orally, and morphine sulfate, 0.1 mg/kg intramuscularly, given approximately 90 min prior to the induction of anesthesia. ECG leads II and V5, and radial and pulmonary arterial pressures were monitored continuously in all patients. Cardiac output was measured in triplicate by the thermodilution method. Five minutes prior to the induction of anesthesia, Group E patients received esmolol (supplied in 10-ml ampuls containing esmolol HCl 100 mg/ml in 10% propylene glycol USP, 10% alcohol USP, and water for injection USP), 500 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 2 min, followed by an infusion of 200 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which was continued until 5 min after mediastinal dissection. Group P patients received comparable volumes of the vehicle under blinded conditions.

In all patients, anesthesia consisted of fentanyl, 50 μg/kg, administered over 20 min, followed by a continuous infusion of 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Pancuronium, 0.1 mg/kg, was given 7 min after the beginning of induction to facilitate tracheal intubation. All patients were intubated exactly 10 min after the beginning of induction, which corresponded to a fentanyl dose of 25 μg/kg. Increases in mean arterial pressure (MAP) greater than 20% of control were treated with enflurane. Hemodynamic measurements were made prior to the esmolol or placebo infusion, designated as control (C); 5 min after initiating the esmolol or placebo infusion (T_1), 1 min prior to intubation (T_2), and 2 min after each of the following: intubation (T_3), skin incision (T_4), sternotomy (T_5), and mediastinal dissection (T_6). Hemodynamic measurements consisted of heart rate, systolic and diastolic blood pressures, MAP, cardiac output, pulmonary capillary wedge pressure (PCWP), pulmonary arterial systolic and diastolic pressures, mean pulmonary artery pressure (MPAP), and central venous pressure (CVP). Systemic vascular resistance (SVR) was calculated. Data are expressed as mean ± SEM and were evaluated for statistical significance by two-way analysis of variance using Tukey's *W*-test of multiple comparisons (9).

Table 1. Demographic Data

	Group S (standard therapy; *n* = 10)	Group E (esmolol; *n* = 10)	Group P (placebo; *n* = 10)
Age (yr)			
mean	57	59	54
range	39–72	47–72	38–67
Weight (kg)			
mean	72	87	87
range	43–120	58–112	76–100
Height (cm)			
mean	171	173	173
range	150–190	158–195	162–187
Antianginal therapy			
β-blockers[a]	6	7	9
Calcium channel blockers[a]			
Nifedipine	5	3	5
Diltiazem	3	1	5
Verapamil	1	1	0
Nitrates[a]	4	7	6

[a] Numbers of patients

Results

Patients in the three groups had similar demographic data (age, weight, height, and preoperative medications) (Table 1). There were no significant differences between the groups in terms of the numbers of patients receiving nitrate therapy, calcium channel blockers, or β-adrenergic receptor antagonists. The hemodynamic data, both measured and derived at the various periods of the study, are shown in Table 2. Group E patients had no significant change in heart rate during induction, intubation, skin incision, sternotomy, or mediastinal dissection (Fig. 1). Group P patients had statistically significant increases above control levels in heart rate 1 min prior to intubation, 2 min after intubation, after sternotomy, and after mediastinal dissection. Group S patients also had statistically significant increases in heart rate before and after intubation, and after sternotomy and mediastinal dissection. The differences in heart rate between Groups E and P at the T_3–T_5 measurements were also statistically significant.

There were no statistically significant changes in MAP, cardiac output, or SVR in any group or between groups for any of the measurements (Table 2). A similar number of patients in all three groups required enflurane to lower MAP (4 in Group E, 5 in Group P, and 6 in Group S). A transient statistically signi-

Table 2. Hemodynamic Data

	C	T1	T2	T3	T4	T5	T6
Heart rate (beats/min)							
Group E	69.4 ± 4.2	61.4 ± 3.1	67.8 ± 3.0^{b}	70.9 ± 3.3^{b}	64.6 ± 1.9^{a}	66.4 ± 2.4^{b}	67.2 ± 2.3^{b}
Group P	72.5 ± 4.3	67.6 ± 4.5	87.4 ± 2.9^{d}	91.2 ± 4.3^{d}	80.1 ± 3.5	86.1 ± 4.6^{d}	89.7 ± 4.2^{d}
Group S	65.7 ± 3.7	—	75.4 ± 5.9^{d}	79.0 ± 6.6^{d}	68.2 ± 4.3	75.0 ± 5.6^{c}	79.8 ± 5.1^{d}
Mean arterial pressure (mm Hg)							
Group E	92.9 ± 3.8	92.4 ± 5.1	88.3 ± 5.2	95.2 ± 7.1	96.6 ± 7.3	97.3 ± 6.9	91.2 ± 4.8
Group P	96.8 ± 4.9	97.5 ± 5.1	88.9 ± 3.8	98.2 ± 4.9	94.8 ± 4.9	99.0 ± 4.9	89.2 ± 4.4
Group S	83.8 ± 3.3	—	86.4 ± 4.1	93.1 ± 5.1	87.7 ± 4.0	92.4 ± 4.7	95.0 ± 5.3
Cardiac output (L/min)							
Group E	6.21 ± 0.77	5.50 ± 0.66	—	5.83 ± 0.54	5.18 ± 0.46	5.70 ± 0.56	5.61 ± 0.59
Group P	5.76 ± 0.28	5.45 ± 0.41	—	6.53 ± 0.35	5.37 ± 0.32	5.85 ± 0.19	5.92 ± 0.43
Group S	5.22 ± 0.55	—	—	5.95 ± 0.75	5.34 ± 0.55	5.51 ± 0.56	5.6 ± 0.50
Pulmonary capillary wedge pressure (mm Hg)							
Group E	11.2 ± 0.6	12.4 ± 1.0	—	15.5 ± 1.7^{d,a}	12.8 ± 1.0^{a}	12.8 ± 1.2^{a}	12.7 ± 1.2^{a}
Group P	13.1 ± 1.0	12.8 ± 0.7	—	11.7 ± 0.6	9.6 ± 0.5^{c}	9.6 ± 1.0^{c}	9.4 ± 0.7^{d}
Group S	13.2 ± 1.4	—	—	14.5 ± 1.4	14.7 ± 1.5^{a}	15.4 ± 1.6^{a}	15.5 ± 1.5^{a}
Systemic vascular resistance (dynes·sec^{-1}·cm^{-5})							
Group E	1110 ± 128	1233 ± 148	—	1216 ± 181	1375 ± 187	1289 ± 135	1223 ± 130
Group P	1223 ± 86	1330 ± 69	—	1114 ± 109	1308 ± 105	1303 ± 85	1250 ± 114
Group S	1287 ± 163	—	—	1336 ± 233	1309 ± 192	1382 ± 218	1234 ± 95

Abbreviations: C, control measurements; T1, 5 min after initiating esmolol or placebo infusion; T2, one min prior to intubation; T3, 2 min after intubation; T4, 2 min after skin incision; T5, 2 min after sternotomy; T6, 2 min after mediastinal dissection; Group E, esmolol; Group P, placebo; Group S, standard therapy.

[a] $P \leq 0.05$ vs Group P
[b] $P \leq 0.01$ vs Group P
[c] $P \leq 0.05$ vs control
[d] $P \leq 0.01$ vs control

ficant increase in PCWP after intubation in Group E patients occurred, but it was not accompanied by ECG changes and did not require treatment (Fig. 2). A slight, statistically insignificant increase in PCWP also occurred at intubation in Group S patients. Group P patients had no significant changes in PCWP at intubation, but they did have a statistically significant decrease in PCWP at skin incision, sternotomy, and mediastinal dissection. Pulmonary capillary wedge pressure was significantly higher in Group E than Group P at all times, from T_3–T_6. Similarly, PCWP was significantly higher in Group S than in Group P at T_4–T_6.

Three patients in Group S developed ischemic ECG changes prior to cardiopulmonary bypass. In one patient the ECG changes occurred after intubation and were associated with an increase in heart rate from 75 to 98 beats/min. In another patient the ECG changes occurred after sternotomy and were associated with an increase of heart rate from 80 to 102 beats/min. Both of these patients were treated with intravenous nitroglycerin and propranolol. The third patient developed ECG changes during mediastinal dissection without any associated increase in heart rate or MAP and was treated with intravenous nitroglycerin and rapid institution of cardiopulmonary bypass. Nine of these patients developed perioperative myocardial infarctions. No ischemic ECG changes occurred in Group P or Group E patients.

Discussion

The purpose of our study was to determine whether esmolol could attenuate sympathomimetic responses to anesthetic induction, tracheal intubation, and surgical stimulation during fentanyl–oxygen–pancuronium anesthesia. Esmolol had been previously shown to attenuate sympathomimetic responses to intubation in patients lightly anesthetized by a variety of techniques. In one study, anesthesia consisted of only diazepam, 0.5 mg/kg, and 50% (N_2O) in combination with pancuronium (6). In another study, anesthesia was induced with ketamine, a known sympathomimetic drug (7,10). In both studies similar increases in serum catecholamine concentrations occurred after intubation in both the esmolol and control groups; however, only the placebo group had increases in heart rate. In the former study, the increases in heart rate were associated with significant increases in plasma norepinephrine levels in the control group but not in the esmolol group. This result indicates that esmolol works at the receptor (β) level in maintaining stable hemodynamics. We chose fentanyl and pancuronium for the present study because they are widely used

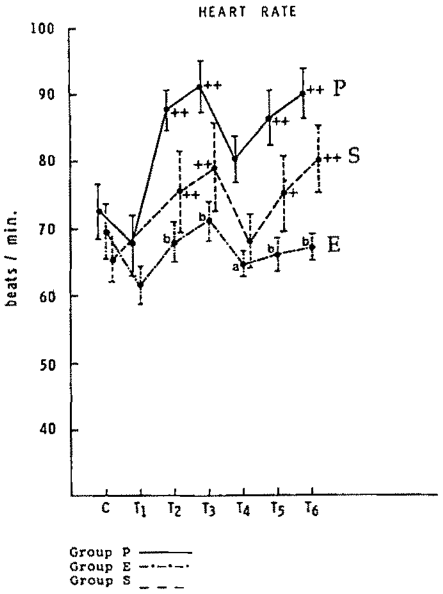

Figure 1. Heart rate after anesthetic induction, tracheal intubation and surgical stimulation. Abbreviations: C, control measurements; T_1, 5 min after initiating esmolol or placebo infusion; T_2, 1 min prior to intubation; T_3, 2 min after intubation; T_4, 2 min after skin incision; T_5, 2 min after sternotomy; T_6, 2 min after mediastinal dissection.

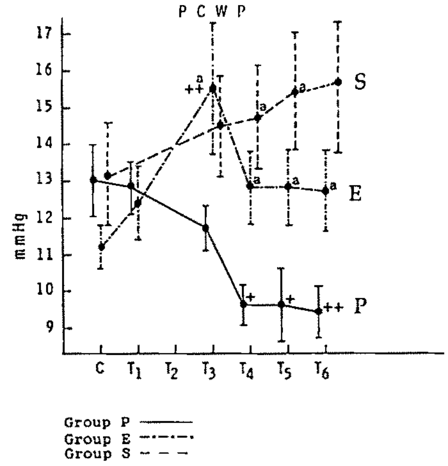

Figure 2. Pulmonary capillary wedge pressure associated with anesthetic induction, tracheal intubation, and surgical stimulation. Abbreviations as in Figure 1.

for anesthesia in patients undergoing aortocoronary bypass surgery.

There were no significant changes in heart rate 5 min after beginning the esmolol infusion (T_1), which can probably be explained by the slow control heart rate of these patients (mean, 69 beats/min). This slow heart rate may have been due to residual β-blockade despite discontinuation of therapy the night before surgery. Girard et al. also failed to see a significant decrease in heart rate when esmolol was added to high-dose fentanyl anesthesia in the absence of noxious stimulation (anesthetic or surgical) in patients undergoing aortocoronary bypass surgery (11). Their patients also had a slow heart rate initially (60 beats/min) despite discontinuation of oral β-blockers for at least 8 hr prior to the study. In contrast, Menkhaus et al. found that heart rate prior to intubation had no effect on subsequent heart rate responses (6). These investigators began their esmolol infusions after diazepam, N_2O, and pancuronium, 0.1 mg/kg, had been administered. Gold et al., on the other hand, found a decrease in heart rate from 80 to 70 beats/min 4 min after esmolol, 300 $\mu g \cdot kg^{-1} \cdot min^{-1}$, in the absence of stimulation (7). The authors do not mention preoperative medications (β-blockers?) or the type of surgery in their report. Korenaga et al. excluded patients on β-blocker therapy from their study and reported a slight and statistically insignificant decrease in heart rate from 83 to 70 beats/min during infusion of esmolol 500 $\mu g \cdot kg^{-1} \cdot min^{-1}$ prior to anesthetic induction (8).

Similar to other investigators using various anesthetic techniques, we found that esmolol attenuated the heart rate responses to intubation. The increases in heart rate in our placebo and standard therapy groups 1 min prior to intubation were most likely a result of the pancuronium given to facilitate tracheal intubation. Pancuronium is commonly used with high-dose fentanyl anesthesia to counteract the vagally mediated bradycardia caused by fentanyl. However, significant increases in heart rate accompanied by ischemic ECG changes may occur with this technique (12). Such increases in heart rate were prevented by esmolol in our study and attenuated in the high-dose esmolol group in the study by Menkhaus et al. in which anesthesia was induced with diazepam–N_2O followed by pancuronium prior to administration of esmolol (6).

Thompson et al. reported that fentanyl–pancuronium anesthesia was associated with significantly greater heart rate responses (mean ± SD, 76 ± 24 beats/min) than fentanyl–metocurine (56 ± 8 beats/min) or fentanyl–metocurine–pancuronium anesthesia (57 ± 8 beats/min) (12). Three of the 12 patients in the fentanyl–pancuronium group had ischemic ECG changes associated with the increased heart rate. There were no ischemic ECG changes in the fentanyl–metocurine or fentanyl–metocurine–pancuronium group. The results of that study have caused some investigators to conclude that a heart rate above 70 beats/min is undesirable in patients at risk of myocardial ischemia (13). We did not observe any ischemic

ECG changes in our Group P or Group E patients during anesthesia despite mean heart rates up to 91 beats/min. All of the ischemic episodes occurred in our Group S patients despite the fact that their mean heart rate was lower than those of Group P patients at all times.

Heart rates continued to rise in our placebo and standard therapy groups at intubation. Although heart rates returned to control values by the time of skin incision, they increased again in both groups with sternotomy and with mediastinal dissection. It is important to note that several minutes elapsed between endotracheal intubation and skin incision in these patients, during which time the Foley catheter was inserted and the patient was prepared and positioned for surgery.

There were no statistically significant changes in MAP in any group at any of the measurements in the present study. Unlike other studies in which significant increases in MAP occurred in control patients at intubation (6–8), our control patients (Groups P and S) had no significant increases in MAP during intubation. This finding may be a reflection of the deeper level of anesthesia maintained in our study by the continuous infusion of fentanyl.

The increase in PCWP seen in our esmolol patients 2 min after intubation deserves comment. Increases in PCWP, presumably due to regional myocardial dysfunction, have been reported to be an earlier indicator of myocardial ischemia than ECG changes (14). However, patients in our study who developed increased PCWP did not have any associated ischemic ECG changes, nor did they have any other indicators of increased myocardial oxygen demand, i.e., increases in heart rate or MAP. The transient increase in PCWP seen in our patients might have represented mild myocardial depression caused by esmolol, which has been previously reported when esmolol was added to fentanyl anesthesia (11). It should be pointed out that the Group E patients by chance had a lower control PCWP than Group P or S patients. Although the increase in PCWP in Group E patients averaged only 4 mm Hg, it would not have been as dramatic had the control PCWP been identical to Group S or Group P. It was also interesting to note in this study that the other group receiving β-blockers on the morning of surgery (i.e., Group S) also had an increase in PCWP at intubation, although this was not statistically significant.

Although we did not perform a pharmacokinetic analysis of esmolol in our study, the pharmacokinetics of esmolol have been evaluated in awake and anesthetized patients (6,11,15). Sum et al. evaluated the pharmacokinetics of esmolol in eight male volunteers (15). They reported distribution and β-elimination half-lives of 2.03 and 9.19 min respectively. The clearance of esmolol averaged 285 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, which is roughly 14 times hepatic blood flow and four times normal cardiac output, suggesting nonhepatic routes of elimination (i.e., ester hydrolysis in plasma).

The ability of esmolol to attenuate hemodynamic responses to noxious stimulation should not be surprising when one considers previous reports of other β-adrenergic receptor antagonists used for this purpose. Prys-Roberts et al. reported that oral or intravenous practolol was effective in attenuating heart rate and blood pressure responses to tracheal intubation in patients anesthetized with thiopental or althesin (16). Kopriva et al. reported that patients regularly taking oral propranolol showed a significant attentuation of heart rate but not blood pressure responses to intubation (17). Still et al. recently correlated plasma propranolol levels in patients regularly taking propranolol to hemodynamic responses to stressful events (intubation, sternotomy, skin incision, sternal retraction) during aortocoronary bypass surgery (18). They reported an inverse correlation between log serum propranolol levels and magnitude of heart rate, MAP, PCWP, and cardiac index (CI) responses to stressful stimulation in patients anesthetized with morphine–diazepam–pancuronium–halothane. As predicted by Sills et al., our patients who were maintained on their cardiac drugs (Group S) had heart rate responses that were in between the placebo and esmolol groups.

In summary, we have shown that esmolol was effective in attentuating hemodynamic responses to noxious stimulation during coronary artery surgery performed under fentanyl–oxygen–pancuronium anesthesia. The unique pharmacokinetic properties of esmolol may increase the ease and safety of producing β-adrenergic receptor blockade during aortocoronary bypass surgery where rapid modifications of the intensity of pharmacologic effect may be needed to match changing sympathetic and hemodynamic conditions.

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ANESTH ANALG 1986;65:457–62

Intracellular Mechanism of Action of Isoflurane and Halothane on Striated Muscle of the Rabbit

Judy Y. Su, PhD, and Janet G. Bell, BS

SU JY, BELL JG. Intracellular mechanism of action of isoflurane and halothane on striated muscle of the rabbit. Anesth Analg 1986;65:457–62.

Studies were conducted on the effects of isoflurane and halothane on intracellular mechanisms of striated muscle contraction: Ca^{2+} activation of the contractile proteins and Ca^{2+} uptake and release from the sarcoplasmic reticulum. Functionally skinned muscle fibers (sarcolemma disrupted by homogenization) from isolated papillary muscle (PM), soleus (SL) (slow-twitch skeletal muscle), and adductor magnus (AM) (fast-twitch skeletal muscle) of rabbits were mounted on a photodiode tension transducer. They were immersed in control solution (saturated with N_2), then in test solution (saturated with anesthetic–N_2 mixture), and in control solution again. The following two studies were carried out: 1) in the study of Ca^{2+}-activated tension development of the contractile proteins, free Ca^{2+} concentration in the bathing solution was controlled by the use of a high EGTA (7 mM), and 2) in the study of Ca^{2+} uptake and release from the sarcoplasmic reticulum (SR), Ca^{2+} was loaded into the SR and released with caffeine and the resulting tension transients were measured. Isoflurane (1–4%) decreased (6–9%) the maximal Ca^{2+}-activated tension development in PM and SL but more in PM than in SL. In AM, however, isoflurane and halothane (1–3%) produced no change. Isoflurane decreased submaximal Ca^{2+}-activated tension development in PM, but effected no change in it in SL. Isoflurane and halothane increased the tension development in AM to the extent of producing a shift to the left in the pCa-tension curves of ≤ 0.1 pCa unit. Isoflurane decreased by 16% Ca^{2+} uptake by the SR in PM at 3% concentration, increased uptake 110–143% in SL at 1–3%, and increased by 72–121% and 15–73% Ca^{2+} release from the SR in SL and AM, respectively. With submaximal caffeine concentration at 2 mM, isoflurane (4% only) increased by 21% Ca^{2+} release from the sarcoplasmic reticulum in PM. Halothane (1–3%) decreased by 19–37% Ca^{2+} uptake and increased by 38–75% Ca^{2+} release from the SR in skinned fibers of AM. We conclude that isoflurane and halothane have similar intracellular mechanisms of action in striated muscle. Isoflurane-induced decreases in submaximal and maximal Ca^{2+}-activated tension development and in Ca^{2+} uptake by the sarcoplasmic reticulum in PM could partially contribute to decreased myocardial contractility. The increases in Ca^{2+} release from the SR produced by isoflurane and halothane in SL and AM could contribute to increased muscle contraction.

Key Words: ANESTHETICS, VOLATILE—halothane, isoflurane. MUSCLE, SKELETAL—contractility. IONS—calcium.

Halothane, enflurane, and isoflurane are halogenated inhalation anesthetics with direct negative inotropic effects (1,2). The mechanism of action of halothane and enflurane has been shown to be related mainly to inhibition of Ca^{2+} uptake by the sarcoplasmic reticulum (3,4) and partly to inhibition of Ca^{2+} activation of the contractile proteins (4,5,6), possibly by decreasing the Ca^{2+} current through the sarcolemma (7,8). The decreased Ca^{2+} uptake by the SR is at least partly due to increased Ca^{2+} release from the SR (3,4). As in cardiac muscle, in soleus (slow-twitch skeletal) muscle halothane also increases Ca^{2+} release from the SR in skinned fibers (9), which could contribute to increased twitch tension (10). The similarity in intracellular mechanisms of action between halothane and enflurane on cardiac muscle led us to hypothesize that isoflurane may have similar mechanisms of action on contractile proteins and sarcoplasmic reticulum of cardiac muscle. To test this hypothesis, we studied the effects of isoflurane on functionally skinned myocardial and skeletal fibers. We also studied the effects of halothane on fast-twitch skeletal muscle to determine whether similar mechanisms of action obtain.

Methods

Functionally Skinned Fiber Preparation

The functionally skinned fiber preparation, described by Kerrick and Krasner using skeletal muscle (11), has

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Address correspondence to Dr. Su, Department of Anesthesiology, RN-10, University of Washington, Seattle, WA 98195.

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been used extensively in our laboratory in studies on pharmacologic agents (3–5,9). Right ventricular papillary muscle (PM) and soleus (SL, slow-twitch) and adductor magnus (AM, fast-twitch) skeletal muscles were isolated from New Zealand male white rabbits (2–2.5 kg) killed by cervical dislocation. Pieces of the muscle were homogenized (sarcolemma disrupted) in relaxing solution (no added calcium and 7 mM EGTA). Single fibers from the skeletal muscles and a fiber bundle (approximately 20–30 μm thick, 100 μm wide, and 1 mm long) from the papillary muscle were dissected from the homogenate under a Zeiss stereo microscope and mounted on two pairs of forceps. One end was fixed and the other was attached to a photodiode tension transducer, as described by Hellman and Podolsky (12). The resting tension of the preparation was adjusted with a micrometer until the concavity disappeared (about 2.2 μm of sarcomere length) (13).

Bathing Solution

The ionic composition of the bathing solution was derived from a computer program calculated from the binding constants of the ions used (14). The bathing solution contained $[K^+ + Na^+]$, 70 mM; $MgATP^{2+}$, 2 mM; Mg^{2+}, 0.1 or 1mM; creatine phosphate, 2 mM; [EGTA] total 0.05–7 mM (described below); free $[Ca^{2+}]$, expressed as pCa $= -\log [Ca^{2+}]$ (M), greater than 8, or 7–3.8 (depending on the study described below); methanesulfonate or propionate (major anion); imidazole, 70–80 mM; pH of 7.00 ± 0.02; and ionic strength of 0.15 at 23 ± 2°C. The solution was made with distilled, deionized water. Total calcium concentration in each solution was assayed by an atomic absorption spectrophotometer (Hitachi 180-70, Zeaman Effect).

Control solutions were saturated with 100% N_2 and test solutions with anesthetic–N_2 mixture. Halothane and isoflurane concentrations in the test solutions were assayed by gas chromatograph (15) and expressed as partial pressure in percent of one atmosphere.

Ca^{2+}-Activated Tension Development of the Contractile Proteins

The free calcium concentration in the bathing solution was controlled with high EGTA (7 mM), a calcium buffer; thus the small amount of calcium uptake or release from the SR would not interfere with the tension development.

The preparation was activated with one of the submaximal Ca^{2+} concentrations (pCa from 6.0 to 5.0) followed by a maximal Ca^{2+} concentration (pCa 3.8) and relaxed between contractions with relaxing solution (pCa > 8). The experimental protocol consisted of immersing the fiber preparation in control solution, then in test solution, and then in control solution again (Fig. 1). The height of Ca^{2+}-activated tension development from base line to steady state was calculated as a percentage of maximal Ca^{2+}-activated tension development. The test result was compared with that of the mean of two bracketing controls (before and after the test) by Student's *t*-test for paired data (16). $P < 0.05$ was regarded as statistically significant.

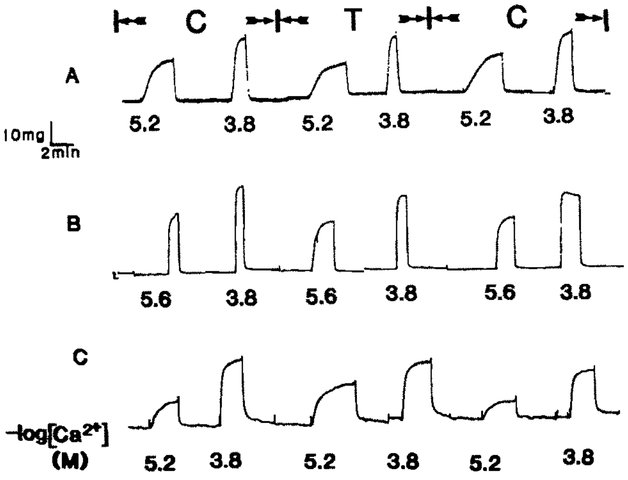

Figure 1. Tracings showing the effects of 3% isoflurane (**A** and **B**) and 2% halothane (**C**) on Ca^{2+}-activated tension development of the contractile proteins in papillary muscle (**A**), soleus (**B**) and adductor magnus (**C**). Top: C, control; T, test (isoflurane or halothane).

Ca^{2+} Uptake and Release from the Sarcoplasmic Reticulum with a Caffeine-Induced Tension Transient

The method of studying Ca^{2+} uptake or release from the SR has been described previously (3). Ca^{2+} was loaded into the SR and released with 25 mM caffeine with five different solutions. The preparation was immersed sequentially in the following solutions (with changed chemical composition in parentheses): solution 1 (25 mM caffeine, 7 mM EGTA, no added Ca^{2+}), to empty the Ca^{2+} from the SR; solution 2 (7 mM EGTA, no added Ca^{2+}), to wash away caffeine in the fibers; solution 3 (pCa 6.5, 7 mM EGTA), to rapidly load the Ca^{2+} into the SR; solution 4 (pCa 7.0 for PM and SL, pCa 6.5 for AM, 0.05 mM EGTA), to wash away the EGTA in the fibers; and solution 5 (pCa 7.0 for PM and SL, pCa 6.5 for AM, 0.05 mM EGTA, 25 mM caffeine), to release Ca^{2+} from the SR and produced in a tension transient (Fig. 2). The fiber preparation was immersed in each solution for 2 min except in solution 3 in which it was immersed for 3 min.

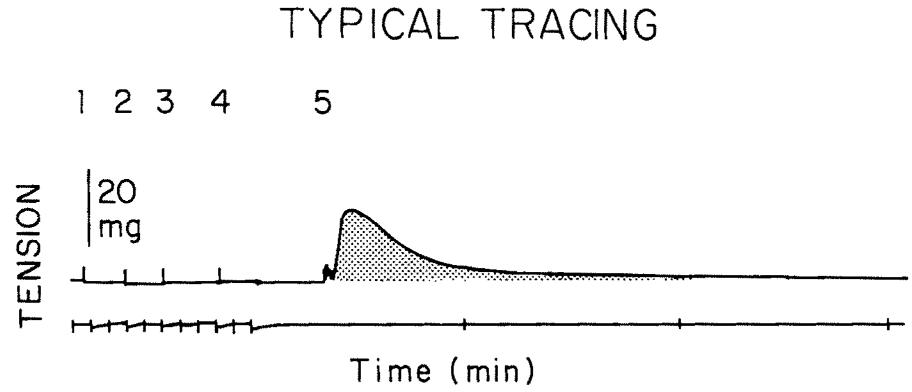

Figure 2. Typical tracing showing caffeine-induced tension transient. 1–5 are solution artifacts, and the compositions of the five solutions are described under Methods. The area of the tension transient is shown with dots.

Table 1. Effects of Isoflurane and Halothane on the Maximal Ca^{2+}-Activated Tension Development (pCa 3.8)

Anesthetic	Papillary muscle[a]	Soleus[a]	Adductor magnus[a]
Isoflurane (percent)			
1	92 ± 1.1 (11)[b]	100 ± 2.0 (13)	98 ± 1.9 (12)
2	93 ± 0.6 (16)[b]	95 ± 2.1 (12)	98 ± 1.6 (12)
3	93 ± 0.8 (19)[b]	94 ± 1.1 (13)[b]	100 ± 2.2 (18)
4	91 ± 1.4 (20)[b]	—	—
Halothane (percent)			
1	—	—	100 ± 1.8 (12)
2	—	—	98 ± 1.5 (12)
3	—	—	104 ± 3.1 (10)

[a] The values are percent of control expressed as mean ± SEM (n).
[b] $P < 0.05$ compared with control by Student's t-test for paired data.

The effect of the anesthetic–N_2 mixture was studied under three conditions: 1) the "uptake" phase, consisting of immersions in solutions 3 and 4, 2) the "release" phase of immersion in solution 5, and 3) the "uptake-and-release" phase, of immersions in solutions 3 through 5. The fiber preparation was preincubated in solution 2 for conditions 1 and 3. The experimental protocol consisted of immersing the preparation in control solution (saturated with 100% N_2), then in test solution (saturated with anesthetic–N_2 mixture under one of the above conditions), and then in control solution again. The area of tension transient was analyzed as an estimate of the amount of Ca^{2+} release from the SR (17). The test result was compared with the mean of two control results by Student's t-test for paired data. $P < 0.05$ was regarded as statistically significant.

Results

Effects of Isoflurane and Halothane on Ca^{2+}-Activated Tension Development of the Contractile Proteins

Isoflurane (1–4%) slightly but significantly decreased (7–9%) the maximal Ca^{2+}-activated tension development of the contractile proteins in PM and SL, but did not significantly change it in adductor magnus (Table 1).

Both isoflurane and halothane (1–3%) affected the submaximal Ca^{2+}-activated tension development of the contractile proteins differently in these three muscle types: they slightly decreased it in PM, produced no change in it in SL, and increased it in AM (Figs. 3, 4, 5, 9). Thus $[Ca^{2+}]$-tension curves were shifted to the right in PM and to the left in AM. At 3% isoflurane or halothane, an approximate shift of ≤0.1 pCa units at half-maximal Ca^{2+}-activated tension development was observed.

Effects of Isoflurane and Halothane on Caffeine-Induced Tension Transient Due to Ca^{2+} Uptake or Release from the Sarcoplasmic Reticulum

Isoflurane decreased Ca^{2+} uptake 15 and 25% in PM at 3 and 4% concentrations, respectively (Fig. 6); increased 110, 100, and 143% in SL at 1, 2, and 3% concentrations, respectively; and did not change it in AM (Fig. 7). Isoflurane (1, 2, and 3%) increased Ca^{2+} release from the SR in SL (72, 112, and 121%, respectively) and in AM (15, 39, and 73%, respectively) (Fig. 7) but did not significantly change it in PM (Fig. 6). At 4% concentration, however, isoflurane in-

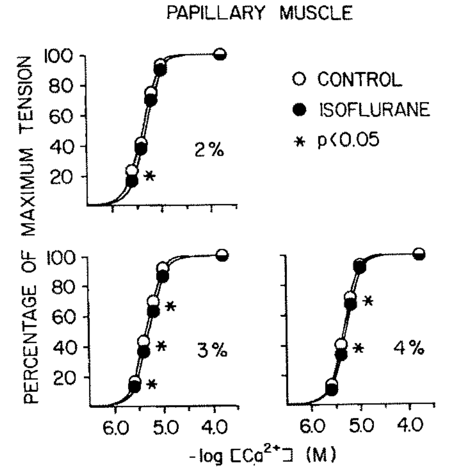

Figure 3. Effects of isoflurane (2, 3, and 4%) on the [Ca^{2+}]-tension relationship (normalized to 100% as maximal tension for both control and isoflurane) of skinned papillary muscle fibers. Each point represents the mean of at least six preparations from at least three rabbits. *$P < 0.05$ compared with control by Student's *t*-test for paired data.

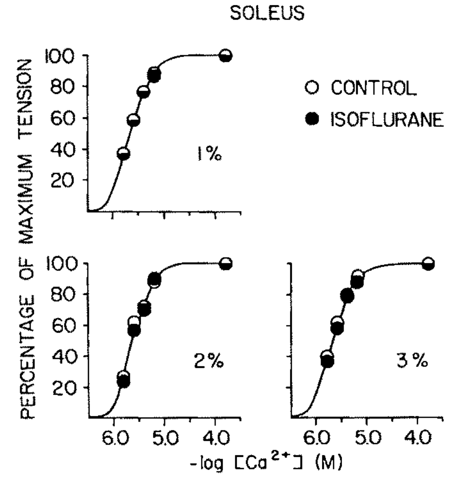

Figure 4. Effects of isoflurane (1, 2, and 3%) on the [Ca^{2+}]-tension relationship (normalized to 100% as maximal tension for both control and isoflurane) of skinned fibers from soleus. Each point represents the mean of at least five preparations from at least three rabbits. *$P < 0.05$ compared with control by Student's *t*-test for paired data.

creased by 21% Ca^{2+} release from the sarcoplasmic reticulum with caffeine at 2 mM (Fig. 6). The total effect of isoflurane on Ca^{2+} uptake and release was a decrease in PM (Fig. 6) and an increase in AM and SL as predicted (data not shown).

In AM, halothane at 1, 2, and 3% decreased the Ca^{2+} uptake by 19, 35, and 37%, respectively, and increased the Ca^{2+} release by 38, 66, and 75%, respectively. Halothane increased the combined Ca^{2+} uptake and release from the sarcoplasmic reticulum by 31% at 3% concentration (Fig. 8).

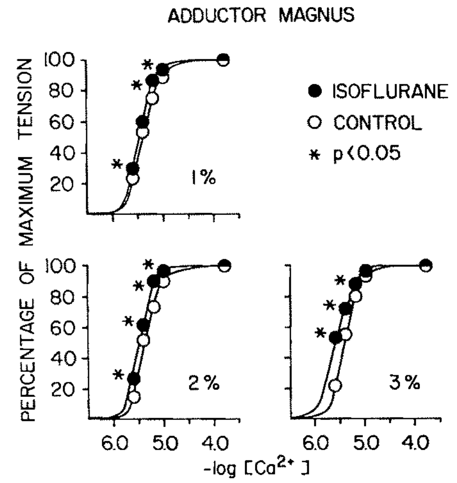

Figure 5. Effects of isoflurane (1, 2, and 3%) on the [Ca^{2+}]-tension relationship (normalized to 100% as maximal tension for both control and isoflurane) of skinned fibers from adductor magnus. Each point represents the mean of at least five preparations from at least three rabbits. *$P < 0.05$ compared with control by Student's *t*-test for paired data.

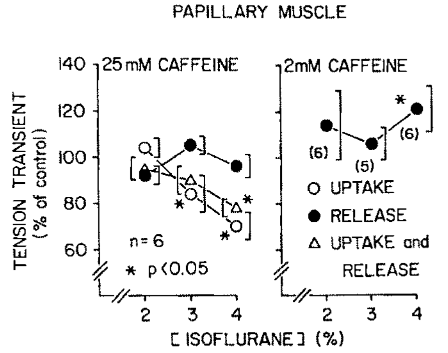

Figure 6. Dose–response relationship of isoflurane on caffeine-induced (25 mM or 2 mM) tension transient of skinned papillary muscle fibers. Each point represents mean ± SEM, and $n = 6$. *$P < 0.05$ compared with control by Student's *t*-test for paired data.

Discussion

This study shows that isoflurane has similar intracellular mechanisms of action to halothane (3,5,9) and enflurane (4) on striated muscles but is not as potent. The decreases in maximal and submaximal Ca^{2+}-activated tension development of the contractile proteins and in Ca^{2+} uptake by the SR produced by isoflurane in skinned fibers of PM could be responsible in part for the isoflurane-induced decreases in myocardial contractility observed by others in isolated intact muscle preparations (2,18). The marked discrepancy between skinned myocardial fibers (Table 1, Figs. 3,6) and isolated intact preparations (2,18) in the degree of depression by isoflurane, in contrast to that by halothane (3) or enflurane (4), could be due to a greater frequency-dependent effect (18). At the phys-

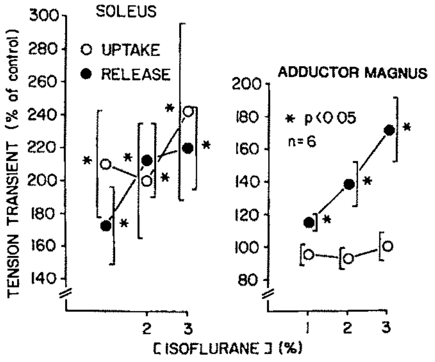

Figure 7. Dose–response relationship of isoflurane on caffeine-induced tension transient of skinned fibers from soleus and adductor magnus. Each point represents mean ± SEM and $n = 6$ for all. $^*P < 0.05$ compared with control by Student's *t*-test for paired data.

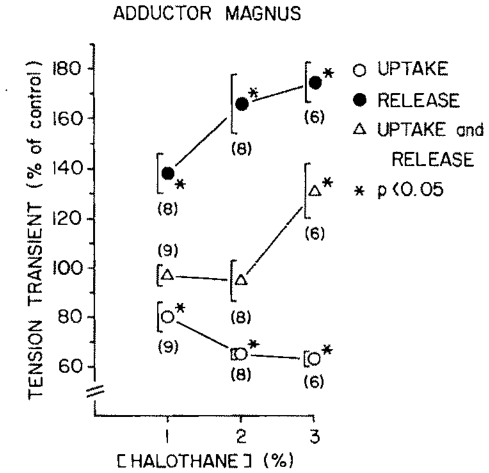

Figure 8. Dose–response relationship of halothane under three conditions on caffeine-induced tension transient in skinned fibers of adductor magnus. Each data point represents mean ± SEM (n). $^*P < 0.05$ compared with control by Student's *t*-test for paired data.

iologic frequency of stimulation (>1 Hz), isoflurane causes much less depression of the peak development tension of isolated intact PM from guinea pigs (18) than at low frequencies. Whether isoflurane has a frequency-dependent effect on contractility of isolated PM from rabbits is not clear.

From the increased submaximal Ca^{2+}-activated tension development of the contractile proteins in AM caused by isoflurane (Fig. 5) and halothane (Fig. 9) and the increased Ca^{2+} release from the sarcoplasmic reticulum in SL (Fig. 7) and in AM (Figs. 7,8) produced by them, we can deduce similar effects on skeletal muscle, leading to increased muscle contraction. We now have evidence of the latter effect for halothane (10) but none as yet for isoflurane.

Our observations on isoflurane-induced decreases in Ca^{2+} uptake by the SR in cardiac muscle and isoflurane- and halothane-induced increases in Ca^{2+} release from the SR in skeletal muscle are consistent with our hypothesis (3,9) that the amount of Ca^{2+} in the SR of cardiac muscle and the amount of Ca^{2+} release from the SR of skeletal muscle are determining factors in contraction and account for the differences in mechanism of contraction between them.

The decreased maximal Ca^{2+}-activated tension development in skinned fibers of PM and SL produced by isoflurane would decrease either the number and/or the strength of cross-bridges interaction. We would expect a decrease in myosin ATPase activity, although no information is available on this aspect. The decreased (Fig. 3) and increased (Figs. 5,9) submaximal Ca^{2+}-activated tension developments in skinned fibers of PM or AM, respectively, could be due to decreases and increases in Ca^{2+} binding to the regulatory protein (troponin C), respectively. No study has been done in this regard.

The decreased Ca^{2+} uptake by the SR in skinned myocardial fibers caused by isoflurane may be caused by decreases in active transport of Ca^{2+} into the sarcoplasmic reticulum associated with decreased ATPase activity, increases in Ca^{2+} release from the SR produced by increasing sarcoplasmic reticulum membrane permeability to Ca^{2+} leading to reduction of Ca^{2+} accumulation in the SR; or both, as shown with halothane (3,9). In contrast, Blanck and Thompson (19,20) reported an increase in Ca^{2+} uptake from isoflurane in isolated cardiac sarcoplasmic reticulum. Whether this increase was coupled with an increase in SR–ATPase activity was not reported. This discrepancy between our results and those of Blanck and Thompson (19,20) could be due to differences in experimental conditions, animal species, or type of sarcoplasmic reticulum studied. The caffeine-induced Ca^{2+} release from the SR of skinned fibers is mainly from terminal cisternae (observed with electron probe microanalysis) (Su and Johnson, unpublished data), whereas in isolated sarcoplasmic reticulum used by Blanck and Thompson (19,20) it is mostly from longitudinal fraction. These different Ca^{2+} storage sites may respond differently to the anesthetic. This speculation remains to be tested.

The increased Ca^{2+} uptake by the SR in skinned fibers of SL produced by isoflurane (Fig. 7) has also been observed with halothane (9). It could be due to increased active transport of Ca^{2+} associated with SR-ATPase activity or to sustained increased sarcoplasmic reticulum membrane permeability to Ca^{2+}, as shown by increased Ca^{2+} release (Figs. 7,8). However, no information is available. In contrast, halo-

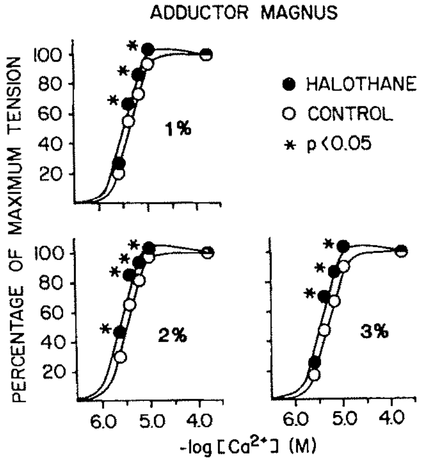

Figure 9. Effects of halothane (1,2, and 3%) on the [Ca^{2+}]-tension relationship (normalized to 100% as maximal tension at pCa 3.8 for both control and halothane) of skinned fibers from adductor magnus. Each data point represents the mean of at least five preparations from at least three rabbits. $^*P < 0.05$ compared with control by Student's *t*-test for paired data.

thane decreased (Fig. 8), and isoflurane did not change (Fig. 7), the Ca^{2+} uptake in skinned fibers of adductor magnus. Whether this effect is due to decreased Ca^{2+} pump activity associated with ATPase activity or to increased Ca^{2+} release (Figs. 7,8) remains to be tested.

In summary, isoflurane decreased the [Ca^{2+}]-tension relationship of skinned fibers from PM, but did not change that from SL, and isoflurane as well as halothane increased that from AM. Isoflurane decreased Ca^{2+} uptake by the SR in skinned fibers of PM and increased Ca^{2+} release from the SR with submaximal caffeine-induced tension transient. Isoflurane as well as halothane increased Ca^{2+} release from the sarcoplasmic reticulum in skinned fibers of SL and AM. Ca^{2+} uptake by the SR was increased by isoflurane in SL, but decreased by halothane in AM. We conclude that isoflurane induces decreases in Ca^{2+} uptake by the SR and in Ca^{2+} activation of the contractile proteins and that these effects could be partly responsible for its negative inotropic action. Isoflurane or halothane increases Ca^{2+} activation of the contractile proteins and Ca^{2+} release from the sarcoplasmic reticulum of SL and AM, and these effects could result in increased skeletal muscle contraction.

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Interaction of Halothane and Verapamil in Isolated Papillary Muscle

Robert A. Caplan, MD, and Judy Y. Su, PhD

CAPLAN RA, SU JY. Interaction of halothane and verapamil in isolated papillary muscle. 1986;65:463–8.

The combined depressant effects of verapamil and halothane on myocardial contractility were studied using isolated papillary muscle from the rabbit. Verapamil alone (0.5 μM) significantly decreased peak developed tension (PDT) by 15 ± 2%, time to peak tension (TPT) by 10 ± 1%, and maximum rate of increase of tension (+dT/dt) by 5 ± 1%, but not maximum rate of decrease of tension (−dT/dt). Halothane alone (0.8%) significantly decreased PDT by 56 ± 2%, TPT by 11 ± 2%, +dT/dt by 53 ± 2%, and −dT/dt by 56 ± 2%. During the exposure period, the combination of verapamil and halothane together produced a simple additive effect (no significant interaction effect by two-way analysis of variance), with PDT decreased by 68 ± 2%, TPT by 20 ± 3%, +dT/dt by 62 ± 2%, and −dT/dt by 65 ± 2%. The reversibility of halothane-induced depression was also studied. Peak developed tension showed complete reversibility 30 min after discontinuing halothane. In the presence of verapamil, however, the reversibility of halothane-induced depression was not complete, and significant residual depression of PDT (19 ± 3%) was observed. We conclude that the acute depressant effect of verapamil plus halothane in isolated papillary muscle is additive, but reversibility of halothane-induced depression may be impaired or prolonged in the presence of verapamil.

Key Words: ANESTHETICS, VOLATILE—halothane. INTERACTIONS, DRUGS—calcium channel blockers, anesthetics. HEART—contractility.

Many patients with cardiovascular disease now take calcium channel blockers on a chronic basis (1). The common hemodynamic effects of calcium channel blockers and inhalational anesthetics are matters of concern for the anesthesiologist. These effects include depression of myocardial contractility, systemic vasodilation, negative chronotropy, and prolongation of atrioventricular conduction (2–6). In our study we have focused on one of these shared actions—depression of myocardial contractility. Recent studies in intact animals (7–9) and man (10) suggest that the combination of calcium channel blockers and inhalational anesthetics results in an additive effect, but the exact nature of the interaction has been difficult to define because of the confounding effects of neurohumoral and vascular reflexes. In an effort to define more precisely this drug interaction, we studied the separate and combined effects of verapamil and halothane in an isolated preparation of rabbit papillary muscle.

Methods

Isolated Papillary Muscle

Rabbits weighing 2.0-2.5 kg were killed by cervical dislocation, and papillary muscles were quickly removed from the right ventricle. Muscles were placed in a Blinks dual tissue bath (11) containing Krebs solution equilibrated with 95% O_2-5% CO_2 at pH 7.4 and 30°C. The Krebs solution was composed of NaCl, 121 mM; KCl, 2.4 mM; $MgSO_4$, 1.2 mM; $NaHCO_3$, 24.8 mM; KH_2PO_4, 1.2 mM; and glucose, 5.6 mM. The lower end of each muscle was fixed to a punctate stimulating electrode, and the upper end was attached to a Statham G7B force transducer with 0000 silk thread. Muscles were paced at 0.2 Hz at twice-threshold voltage with DC square waves of 4-msec duration. Each muscle was stretched to the maximal length (L_{max}) at which peak developed tension (PDT) was greatest. Before any intervention, the muscle preparation was equilibrated for 60 min to allow PDT to reach a steady state. Isometric twitch tension was recorded continuously on a Gould 2400S 4-channel recorder and analyzed for PDT, time to peak tension

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Address correspondence to Dr. Caplan, Department of Anesthesiology, RN–10, University of Washington School of Medicine, Seattle, WA 98195.

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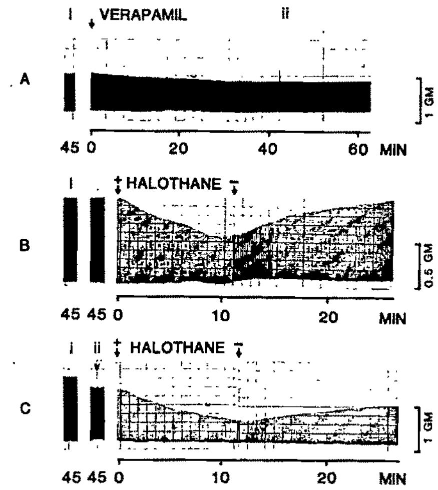

Figure 1. Typical tracings of verapamil and halothane effects on isolated papillary muscle. Initial equilibrated state is indicated by (i). (**A**): Verapamil alone (0.5 μM), added at arrow, produces a gradual 15% decrease in peak developed tension which reaches a steady state by 45 min (ii). (**B**): Halothane alone (0.8%, initiated at "+") results in steady state depression by 12 min. Recovery begins when halothane is discontinued at "−" and continues for 30 min until a steady state is achieved (not shown on this time scale). Note that exposure to halothane alone is conducted after a 45-min waiting period, making the halothane series temporally similar to the series in which papillary muscles are exposed to both verapamil and halothane. (**C**): The interaction of verapamil and halothane is studied by incubating equilibrated papillary muscles in verapamil-containing Krebs solution until a steady state is achieved (ii). Treated muscles are maintained in the verapamil-containing solution and subjected to the same protocol as shown in (**B**). Cross-sectional areas for muscles are 0.50 mm^2 (**A**), 0.92 mm^2 (**B**), and 0.76 mm^2 (**C**).

(TPT), maximum rate of increase of tension (+dT/dt), and maximum rate of decrease of tension (−dT/dt).

Halothane was delivered through a Frazer-Harlake vaporizer using 95% O_2/5% CO_2 as the carrier gas. The partial pressure of halothane in the bathing solution was determined using a Varian 1200 gas chromatograph and the method of Fink and Morikawa (12).

Experimental Design

The basic features of the experimental design are shown in Figure 1 and outlined under the following headings:

Verapamil alone. The depressant effect of verapamil alone (Fig. 1*A*) was defined by incubating papillary muscles in Krebs solution containing 0.5 μM racemic verapamil (Knoll Pharmaceutical). This concentration was chosen because it is located within the clinical range for plasma verapamil levels (0.1–1 μM) in humans (4), and because it produced steady-state depression in the papillary muscle preparation after a 45 min period of equilibration.

Halothane alone. The depressant effect of halothane alone (Fig. 1*B*) was defined by exposing papillary muscles to 0.8% halothane. This concentration is approximately equal to 1 MAC in the rabbit (13) and is also located within the clinical range for maintenance of inhalational anesthesia. To correspond temporally with the set of experiments in which papillary muscles were exposed both to verapamil and halothane (see below), the depressant effect of halothane alone was studied 45 min after the initial equilibration period.

Verapamil plus halothane. To study the combined effects of verapamil and halothane (Fig. 1C), papillary muscles were first incubated for 45 min in Krebs solution containing 0.5 μM verapamil. While remaining in the verapamil-containing bath, these muscles were then subjected to the previously described protocol for halothane exposure.

Halothane recovery. After 12 min of exposure, a steady state of halothane-induced depression was reached. Halothane was then discontinued, and twitch tension was recorded for an additional 30 min, at which time a steady state of recovery was achieved.

Data Analysis

Forty papillary muscles were used, equally divided among the following four groups: drug-free (control) muscles; muscles exposed to verapamil alone (Fig. 1*A*); muscles exposed to halothane alone (Fig. 1*B*); and muscles exposed to both verapamil and halothane (Fig. 1C). In each of these treatment groups, individual papillary muscles were obtained from at least six different animals.

The cross-sectional area of each papillary muscle was calculated as the ratio of wet muscle weight to muscle length (assumed density = 1). To assure adequate tissue oxygenation by diffusion, only those papillary muscles with a cross-sectional area less than 1 mm^2 were included in this study.

Each muscle preparation served as its own control, and results were expressed as percent of control. Three statistical tests were performed on the data as follows: 1) Comparisons between control conditions and single drug effects were made using Student's *t*-test for paired data. 2) Comparisons among different treatment groups were made using one-way analysis of variance. 3) The presence of interaction effects (combined drug effects that could not be explained by simple addition of individual drug effects) was tested using two-way analysis of variance (14). *P* values less than 0.05 were considered significant.

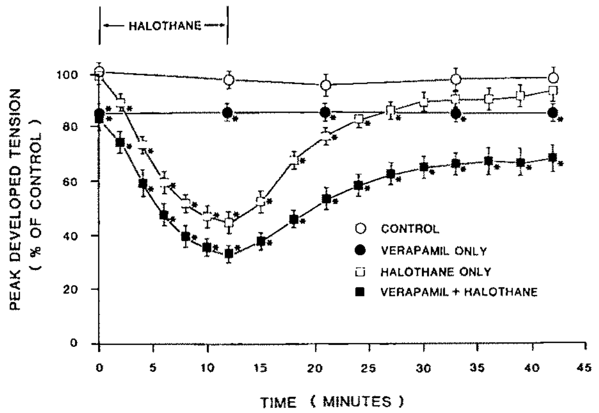

Figure 2. Time-course effects of verapamil and halothane used alone and in combination. All values are mean ± SEM; $n = 10$ for each group. For clarity, intermediate time values are not shown for the control group and for muscles exposed only to verapamil. $^*P < 0.05$ for drug effect vs corresponding time-matched control.

Results

The mean cross-sectional area for papillary muscles ($n = 40$) used in this study was 0.67 ± 0.04 mm^2, and the mean control value for PDT was 1.21 ± 0.13 g/mm^2. Drug-free muscles (controls) showed an average decay in PDT of 5% of control over the time course of this study. During the exposure period, the mean steady-state partial pressure of halothane in the bathing solution was 0.8 ± 0.08%. At the end of the 30-min recovery period, halothane was not detectable in the bath.

The typical effects of verapamil and halothane on PDT are shown in Figure 1. In the presence of 0.5 μM verapamil alone, PDT decreased gradually and reached a steady state by 45 min. In the presence of 0.8% halothane, PDT decreased rapidly and reached a steady state by 12 min. After discontinuing halothane, recovery from halothane-induced depression occurred promptly and reached a steady state by 30 min.

Figure 2 shows the time-course effects of halothane and verapamil on PDT. Verapamil alone decreased PDT to 85 ± 2% of control, halothane alone decreased PDT to 44 ± 2% of control, and the combination of both drugs decreased PDT to 32 ± 2% of control. During the period of halothane exposure, the combined depressant effect on PDT of verapamil plus halothane was almost identical to the effect that would be predicted for the sum of the depressant effects of each drug alone. As shown in Table 1, this observation was confirmed using two-way analysis of variance. At each time-point during halothane exposure, the associated value for F (interaction) was not significant. However, starting with the sixth minute of halothane recovery, the observed values for the combination of verapamil plus halothane were 5–8% lower than the values predicted by simple summation of individual drug effects. The corresponding values for F (interaction) were also significant, suggesting that the interaction of these two drugs impaired or delayed the reversibility of halothane-induced depression during the 30-min recovery period.

The effects of verapamil and halothane on the components of twitch tension at steady-state depression are shown in Figure 3. The only significant effect of verapamil alone was a decrease in TPT to 90 ± 1% of control. The primary effect of halothane alone on the components of twitch tension was a decrease in +dT/dt to 47 ± 2% of control and −dT/dt to 44 ± 2% of control. Halothane alone also produced a small but significant decrease in TPT to 89 ± 2% of control. The combination of verapamil and halothane decreased TPT to 80 ± 1% of control, +dT/dt to 38 ± 2% of control, and −dT/dt to 34 ± 2% of control. Two-way analysis of variance suggested that the combined depressant effect of verapamil plus halothane on the components of twitch tension could be attributed to simple addition of individual drug effects.

The reversibility of halothane-induced depression is shown in Table 2. Thirty minutes after discontinuing halothane, the average value for PDT in papillary muscles exposed to halothane alone showed significantly less depression from the pre-halothane baseline than muscles exposed to both verapamil and halothane. Recovery of TPT after halothane exposure was nearly complete in both the presence and absence of verapamil, but the recovery of +dT/dt and −dT/dt in papillary muscles exposed to the combination of drugs was significantly less. At 30 min of recovery, the observed and predicted effects of verapamil plus halothane on TPT were nearly identical, but +dT/dt and −dT/dt both showed about 10% more depression in the observed values.

Discussion

In this study of myocardial contractility in isolated papillary muscle, the combination of verapamil and halothane produced a simple additive effect during halothane exposure, but a greater-than-additive effect during the period of recovery from halothane-induced depression.

The decrease in twitch tension produced by 1 MAC halothane in our study is approximately 15% greater than that reported by Brown and Crout (15). Although species variation (rabbit vs cat) and different temperatures in the bathing solution (30 vs 37.5°C) may have played some role, this discrepancy probably can be attributed to differences in the measurement of halothane partial pressure. In our study the partial pres-

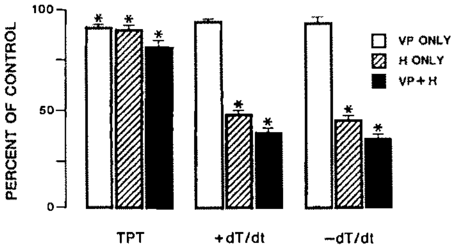

Figure 3. Components of twitch tension at steady-state depression by verapamil (VP) and halothane (H) used alone and in combination (VP + H). All values are mean ± SEM; n = 10.

Abbreviations: TPT, time to peak tension; +dT/dt, maximum rate of increase of tension; −dT/dt, maximum rate of decrease of tension. *$P < 0.05$ vs control.

sure of halothane was measured in the bathing solution, whereas in Brown and Crout's study the partial pressure of halothane was measured in the gas delivered to the bathing solution. When depression of twitch tension in Brown and Crout's study is replotted against partial pressure of halothane in the bathing solution (using a liquid/gas coefficient of 0.8 for physiologic saline at 37°C) (16), our result agrees closely with their linear dose-response curve. Using a similar approach, our result also agrees closely with the observations of Lynch et al. on isolated papillary muscle from the guinea pig (17). The decrease in twitch tension produced by verapamil in this study is comparable with previous studies in isolated papillary muscle from the cat (18) and guinea pig (19).

What mechanism might account for the additive effect of verapamil and halothane that was observed during the period of halothane exposure? In cardiac muscle, verapamil is characterized primarily as an inhibitor of the "slow" calcium current in the cell membrane (20), although intracellular effects have also been suggested (1,18,21). Halothane may alter calcium movement or availability at a variety of sites including the cell membrane (17), the sarcoplasmic reticulum (22–24), and the contractile proteins (24–26). Su and Kerrick (27) have proposed that halothane-induced depression of myocardial contractility results from increased calcium release and decreased calcium uptake by the sarcoplasmic reticulum. The net effect of these changes is depletion of intracellular calcium stores, and subsequently decreased availability of calcium for release to the contractile proteins. If the effects of verapamil on transmembrane flux of calcium and intracelluar calcium stores have reached a steady state prior to the administration of halothane, then exposure to halothane should result in a relatively independent depletion of intracellular calcium. Thus, a simple additive effect would be expected from the combination of verapamil and halothane as used in

Table 1. Time Course of Interaction Effect on Peak Developed Tension

Time (min)	Percent depression observed	Percent depression predicted	F (interaction)
Halothane exposure			
2	26 ± 2.5	26 ± 3.6	0.58
4	41 ± 3.9	43 ± 4.6	0.05
6	53 ± 2.4	57 ± 4.2	0.04
8	61 ± 2.1	65 ± 3.9	0.08
10	65 ± 2.1	70 ± 4.0	0.05
12	68 ± 2.0	72 ± 4.1	0.01
Halothane recovery			
3	63 ± 1.7	66 ± 4.1	0.17
6	54 ± 1.7	50 ± 3.4	5.91[a]
9	48 ± 2.0	41 ± 3.2	9.66[a]
12	43 ± 2.6	35 ± 3.5	7.45[a]
15	39 ± 3.1	33 ± 3.5	6.36[a]
18	37 ± 3.1	29 ± 3.8	7.17[a]
21	36 ± 2.9	29 ± 3.8	6.55[a]
24	35 ± 2.8	28 ± 4.1	6.52[a]
27	36 ± 1.7	28 ± 4.1	6.35[a]
30	34 ± 2.8	26 ± 4.3	6.20[a]

*All values are percent of control, expressed as mean ± SEM; n = 10 for each group. Observed depression represents the depressant effect of verapamil and halothane when used together. Predicted depression is the simple sum of the depressant effect of each drug used alone. The presence of an interaction effect was tested using two-way analysis of variance, with the critical value for $F_{1,36}$ = 4.11.

[a] $P < 0.05$ for interaction effect.

Table 2. Reversibility of Halothane-Induced Depression in Papillary Muscles

	Halothane alone	Verapamil and halothane
PDT	91 ± 3^{a}	$81 \pm 3^{a,b}$
TPT	95 ± 3	99 ± 2
+dT/dt	92 ± 3^{a}	$83 \pm 4^{a,b}$
−dT/dt	94 ± 2	$78 \pm 3^{a,b}$

All values are percent of pre-halothane baseline, expressed as mean ± SEM; $n = 10$ for each group. Measurements obtained just prior to halothane exposure serve as the baseline for calculating completeness of recovery at 30 min.

Abbreviations: PDT, peak developed tension; TPT, time to peak tension; +dT/dt, maximum rate of increase of tension; −dT/dt, maximum rate of decrease of tension.

[a] $P < 0.05$ recovery value vs prehalothane value.

[b] $P < 0.05$ halothane alone vs halothane plus verapamil.

this study. Marshall et al. (28) have recently reported that the combined depressant effect of nifedipine and halothane in isolated rat heart is primarily additive. Although drug interactions are more difficult to characterize in intact animal preparations, studies with verapamil and inhalational anesthetics in dogs (7,8) and humans (10) are also consistent with an additive effect during the phase of myocardial depression.

Differences in the primary sites of action may also provide a mechanism for the interaction effect that was observed during the phase of halothane recovery. Unlike the halothane exposure phase, in which depletion of intracellular calcium is a relatively independent event, repletion of intracellular calcium stores during halothane recovery may depend upon access to extracellular calcium. Thus in the presence of verapamil, a reduction in the flow of calcium across the cell membrane may delay or impair the restoration of intracellular stores. A recent observation by Lynch et al. (17) that is consistent with this mechanism is that halothane-induced depression of twitch tension in isolated papillary muscles can be partially antagonized by increased extracellular Ca^{2+}. Furthermore, the mechanism for this partial antagonism appears to be increased entry of Ca^{2+} through the slow channel.

Another factor that may contribute to the observed interaction during the recovery phase is the possibility that verapamil can depress myocardial contractility at intracellular sites (1,18,21). This may be especially important in the setting of prolonged or chronic exposure, as suggested by time-dependent effects that have been observed in electrophysiologic studies of verapamil (29) and its methoxy derivative, D-600 (30,31). The presence of halothane may also increase the permeability of the cell membrane to verapamil. In this situation, the concentration of intracellular verapamil might be significantly increased during the period of halothane exposure, and then "trapped" at a higher concentration after halothane has diffused out of the bathing solution. Thus the interaction effect that we observed during the phase of halothane recovery may be due to a relative excess of intracellular verapamil as well as a relative deficit of intracellular Ca^{2+}.

An interesting feature of this study was that halothane and verapamil each exhibited a distinct pattern of effects on the three components of twitch tension (TPT, +dT/dt, and −dT/dt). Halothane produced significant decreases in all three components. This pattern appears to be typical of the inhalational agents over a wide range of concentrations (15,32). However, verapamil produced an equivalent decrease in both twitch tension and TPT, and thus there was no significant change in +dT/dt. Factors that can affect TPT in the isolated muscle preparation include resting muscle length, frequency of contraction, and action potential waveform (33–35). The first two of these factors were held constant in this study. Although the third factor—action potential waveform—was not recorded here, previous electrophysiologic studies of isolated papillary muscle (18) have demonstrated that verapamil alters the action potential waveform by widening the plateau phase. It is tempting to speculate that the verapamil-induced changes in TPT that we observed were primarily caused by changes in the action potential waveform, but we cannot exclude the possibility of verapamil effects at other cellular sites. It should also be noted that a decrease in the rate of muscle relaxation can have an important mechanical effect on PDT in the isolated muscle preparation. This effect can occur when the reduction in −dT/dt is great enough to produce incomplete relaxation between successive beats, leading to an increase in resting tension and a decrease in peak developed tension. In the present study, however, the change in −dT/dt was not great enough to produce this mechanical effect.

It is important to note that exposure to verapamil in this study occurred only after papillary muscles had been isolated and placed in the tissue bath. Thus the results of this study reflect the relatively acute effects of verapamil and its interaction with halothane. In clinical practice, a roughly equivalent situation might occur if therapy with a calcium channel blocker were initiated shortly before the administration of an inhalational anesthetic. Insofar as the short-term and long-term effects of calcium channel blockade may differ, the applicability of this model in the setting of chronic therapy is less certain. Whether our observation of a significant drug interaction during halothane recovery in isolated papillary muscle has any correlate in the clinical setting (e..g., slower recovery from the cardiovascular effects of inhalational agents in patients receiving calcium channel blockers) is not clear at present. However, the small magnitude of the effect we observed is consistent with the current clinical impression that the combination of these two classes of drugs is well-tolerated in patients with normal left ventricular function (2).

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Effect of Clonidine on Sympathoadrenal Response during Sodium Nitroprusside Hypotension

Byron C. Bloor, PhD, Linda S. Finander, MS, CRNA, Werner E. Flacke, MD, and Aaron Van Etten, MS

BLOOR BC, FINANDER LS, FLACKE WE, VAN ETTEN A. Effect of clonidine on sympathoadrenal response during sodium nitroprusside hypotension. Anesth Analg 1986;65:469–74.

Supplementation of the antihypertensive action of the peripheral vasodilator sodium nitroprusside (SNP) with clonidine, a centrally-acting agent, was studied in ten dogs anesthetized with isoflurane to evaluate the efficacy of clonidine for reducing the amount of SNP required during induced hypotension. The dose of SNP required to lower mean arterial blood pressure (MAP) by 40% was determined prior to the administration of intravenous clonidine (control), and after incremental doses of 1, 4, and 15 μg/kg. After each dose of clonidine, hypotension was induced with SNP and maintained for 30 min, followed by a 30-min recovery period. Plasma levels of norepinephrine (NE) and epinephrine (EPI) were determined before hypotension, at 5 min and 30 min during hypotension, and at 5 min and 30 min during recovery. During the control period (no clonidine), SNP-induced hypotension resulted in increases in plasma catecholamine levels, with larger increases in EPI (from 70 ± 26 to 851 ± 140 pg/ml, at 30 min) than NE (from 171 ± 26 to 334 ± 58 pg/ml, at 30 min). There was no significant difference between the control MAP and the MAP after each incremental dose of clonidine. In these anesthetized dogs with low sympathetic tone there was no significant decrease in EPI levels after administration of up to 20 μg/kg of clonidine. Increasing doses of clonidine correlated inversely with depression in catecholamine output during induced hypotension and the dose of SNP required to produce this hypotension. The cumulative dose of 20 μg/kg of clonidine prevented hypotension-induced increases in circulating catecholamines and decreased the dose requirement of SNP by 81%, suggesting that as much as 80% of the SNP dose is in response to baroreceptor-mediated increase in sympathetic activity. The attenuation of sympathetic discharge by clonidine during anesthesia, without change in resting MAP, makes it a potentially useful ancillary agent for reducing the amount of SNP used to produce controlled hypotension.

Key Words: ANESTHETIC TECHNIQUES—hypotensive. SYMPATHETIC NERVOUS SYSTEM—alpha agonists, clonidine.

Sodium nitroprusside (SNP) is a vasodilator acting directly on the arteriolar and venous smooth muscle used for acute control of blood pressure. It is commonly employed during anesthesia for induction and maintenance of controlled hypotension. Problems associated with SNP usage during anesthesia include resistance and tachyphylaxis (1–4). Increasing the dosage of SNP to maintain desired hypotension may lead to toxic levels of cyanide; high cyanide levels have been implicated in SNP-related anesthetic deaths (2,5). Supplementation of the antihypertensive effect of SNP by adjuvant drugs, including β-adrenergic blockers, ganglionic blocking agents, and other vasodilating drugs, is used to decrease the required SNP dose (6,7).

Physiologically, the normal function of the baroreceptor reflex is to maintain blood pressure at its set point. SNP induces hypotension by direct peripheral vasodilatation. This results in activation of the sympathetic nervous system and a decrease in vagal tone as a compensatory mechanism for maintenance of blood pressure. Heart rate is usually increased with the use of SNP in both dogs and man. During SNP administration, the carotid sinus baroreceptor reflex is well maintained in lightly isoflurane-anesthetized animals. In fact, a large part of the SNP-induced hypotension may be offset by an increase in cardiac output, which is reflected in an increase in heart rate of 50% or more (8). The increase in sympathetic tone also results in activation of the renin/angiotensin system

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Address correspondence to Dr. Bloor, Department of Anesthesiology, CHS BH-961, UCLA School of Medicine, Los Angeles, CA, 90024.

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Table 1. Effect of Clonidine Pretreatment on Values during and after SNP-Induced Hypotension

Clonidine	Control	SNP 5 min	SNP 30 min	Control Δ 30	Rec 5 min	Rec 30 min	SNP dose ug·kg^{-1}·min^{-1}	% of control
Mean arterial pressure (mm Hg)								
0	123 ± 7	79 ± 7	72 ± 4	50 ± 3	102 ± 5	111 ± 5	15 ± 4	100
1	108 ± 5	73 ± 8	66 ± 3	43 ± 2	94 ± 5	111 ± 3	14 ± 4	92
5	112 ± 3	54 ± 6	68 ± 3	44 ± 2	97 ± 4	101 ± 5	8 ± 3[a]	53
20	116 ± 9	62 ± 6	68 ± 6	47 ± 3	94 ± 7	88 ± 7	3 ± 1[c]	18
Heart rate (beats/min)								
0	147 ± 7	154 ± 9	151 ± 9	4 ± 6	149 ± 9	146 ± 9	—	—
1	133 ± 7	147 ± 8	151 ± 10	18 ± 5	141 ± 9	134 ± 8	—	—
5	114 ± 5	130 ± 8	135 ± 11	24 ± 10	120 ± 11	121 ± 11	—	—
20	113 ± 10	122 ± 7	113 ± 6	−1 ± 4	104 ± 6	104 ± 7	—	—
Epinephrine (pg/ml)								
0	70 ± 26	509 ± 110	851 ± 140	781 ± 134	483 ± 117	276 ± 74	—	—
1	169 ± 47	531 ± 126	590 ± 179	421 ± 146[a]	369 ± 104	134 ± 47	—	—
5	53 ± 16[b]	286 ± 122	283 ± 121[c]	231 ± 111[c]	144 ± 60[a]	35 ± 9	—	—
20	22 ± 6[b]	38 ± 22[c]	26 ± 5[c]	5 ± 4[c]	19 ± 4[c]	16 ± 2	—	—
Norepinephrine (pg/ml)								
0	171 ± 26	238 ± 44	334 ± 58	163 ± 54	240 ± 43	199 ± 27	—	—
1	112 ± 17	207 ± 42	266 ± 63	154 ± 59	221 ± 51	119 ± 18	—	—
5	54 ± 13	104 ± 23[a]	147 ± 37[c]	93 ± 41	89 ± 21[b]	71 ± 17[a]	—	—
20	40 ± 12[a]	46 ± 12[c]	41 ± 10[c]	1 ± 5[b]	45 ± 12[c]	51 ± 17[b]	—	—

Data are expressed as mean ± SEM.

Abbreviations: SNP 5 min, 5 min after starting the sodium nitroprusside-induced hypotension; SNP 30 min, 30 min after starting the sodium nitroprusside-induced hypotension; Control Δ 30, change in level at 30 min from control; Rec 5 min, 5 min recovery after termination of SNP infusion; Rec 30 min, 30 min recovery after termination of SNP infusion.

[a] $P < 0.05$ from control (0 μg/kg clonidine).

[b] $P < 0.01$ from control (0 μg/kg clonidine).

[c] $P < 0.001$ from control (0 μg/kg clonidine).

mediated, in part, by a β-adrenergic receptor stimulation. β-Adrenergic receptor blockers such as propranolol have been shown to block this SNP-induced activation (6).

Clonidine is a centrally-acting α-agonist used for its acute and chronic antihypertensive actions (9–11). These actions are mediated through central reduction of sympathetic outflow (10,12–16) and by an action upon neurons in the medulla concerned with cardiovascular regulation (8,16). Clonidine has no direct negative inotropic or chronotropic cardiac effects. To our knowledge, use of clonidine as an adjuvant for reducing the dose of SNP necessary for a given magnitude of hypotension has not been previously reported.

The purposes of this study were: 1) to examine the effects of acutely administered clonidine on SNP-induced hypotension; 2) to determine a dose–response relationship between clonidine and SNP dose reduction (if any); and 3) to examine the effect on the sympathoadrenal system when both drugs are given.

Methods

Anesthesia was induced in ten healthy mongrel dogs (16–23 kg) with intravenous thiopental (15–20 mg/kg), followed by tracheal intubation. The animals were mechanically ventilated to maintain a normal Pa_{CO_2}. Isoflurane in oxygen was maintained at 2.4 vol% end-tidal concentration (approximately 1.5 MAC) during instrumentation of the animals and was later reduced to 1.6% (1 MAC). This was followed by a 30-min stabilization period before the experimental protocol was started. Body temperature was maintained at 38.5 ± 0.5°C by means of a temperature-controlled water blanket. Blood pressure was measured through a femoral arterial cannula connected to a Hewlett–Packard pressure transducer. Mean arterial blood pressure (MAP) was derived electronically. Heart rate and ECG were monitored and heart rate recorded by a cardiotachograph. All cardiovascular measurements were recorded on a direct-writing polygraph (Hewlett–Packard model 7758B). Data were gathered on-line using a Minc 11/23 microcomputer. All cardiovascular data was tabulated at end expiration.

A femoral intravenous catheter was inserted through which all drugs were given. Atropine (0.02 mg/kg) was given every hour. Arterial blood samples for measurements of plasma levels of epinephrine (EPI) and norepinephrine (NE), were drawn at 20 min and 30 min into the 30-min stabilization period. A controlled SNP infusion (Princeton infusion pump) was used to lower MAP by 40% from the control value established during the stabilization period. Arterial blood samples for catecholamine measurements were drawn at 5 min and 30 min after the SNP infusion had begun. The infusion was discontinued after 30 min, and samples were again taken 5 min and 30 min later. Intravenous clonidine, 1 μg/kg at an infusion rate of 0.5 μg/min, was administered. Blood samples were then drawn 5 min and 30 min after administration of the clonidine. Again, a SNP infusion was used to decrease MAP 40% below the level observed after the administration of clonidine, with blood samples for measurement of catecholamine levels obtained at 5 min and 30 min into the SNP infusion and at 5 min and 30 min after its discontinuation. This sequence was repeated after 4 μg/kg (subtotal dose 5 μg/kg) and 15 μg/kg (final total 20 μg/kg) of clonidine, given at the same infusion rate of 0.5 μg/min. Each blood sample was replaced with an equal volume of lactated Ringer's solution. Plasma catecholamine samples were collected on ice in tubes containing 10.5 mg EDTA. The plasma was promptly separated using a refrigerated centrifuge, removed, and stored at −80°C until catecholamine determinations were made. Levels were measured by high performance liquid chromatography with electrochemical detection (17). The level of sensitivity in our laboratory is 20 pg/ml for both NE and EPI, and intra- and inter-assay variability are less than 5 and 6%, respectively.

Sodium nitroprusside was obtained from the UCLA pharmacy at a concentration of 20 mg/ml and diluted to 4 mg/ml for infusion. The SNP solutions were protected from light throughout their use. Clonidine was obtained from Boehringer Ingelheim, and a concentration of 10 μg/ml in saline was prepared daily.

Each dog served as its own control. Values reported are expressed as mean ± SEM. Statistical tests used were analysis of variance for repeated measure and Bonferroni modified *t*-test. The Bonferroni modified *t*-test was used to isolate differences between groups when analysis of variance for repeated measure proved significant. Values of $P < 0.05$ were used as the criterion for statistical significance. Dose–response curves were calculated using regression analysis.

Results

Control MAP was 123 ± 7 mm Hg and control heart rate was 147 ± 7 beats/min ($n = 10$; Table 1). Clonidine in cumulative doses of 1, 5, and 20 μg/kg did not significantly change MAP from the control value in normovolemic animals anesthetized with isoflurane; however heart rate was reduced to 113 ± 10 beats/min by 20 μg/kg of clonidine (Table 1). The resting (control) EPI level (70 ± 26 pg/ml) was not affected by the clonidine treatment. On the other hand, the control NE level (171 ± 26 pg/ml) was reduced by 77% by 20 μg/kg of clonidine ($P < 0.05$) (Table 1).

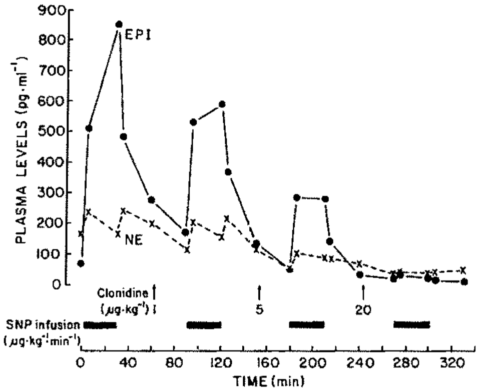

Figure 1. Effect of incremental doses of clonidine on norepinephrine and epinephrine plasma levels during sodium nitroprusside-induced hypotension. Values shown are the mean ± SEM.

The 40% decrease in MAP induced by the SNP infusion during the control period (before clonidine was given) resulted in sympathetic activation, as reflected by a large increase in circulating plasma catecholamine levels. The mean increase in EPI after 30 min hypotension was 781 ± 134 pg/ml, a twelvefold increase over control. The increase in NE was smaller; the mean increase during induced hypotension was 163 ± 54 pg/ml, or almost a doubling of resting levels. This pattern of response (EPI >> NE) remained consistent even after clonidine treatment.

Sympathetic discharge during the induced hypotension was attenuated by clonidine. One μg/kg clonidine had little effect on the hypotension-induced sympathetic discharge; only circulating plasma EPI was significantly reduced at the 30 min point. After the same duration of hypotension, 5 μg/kg clonidine (i.e., 1 + 4 μg/kg) reduced the increase in the EPI levels by 70% (781 to 231 pg/ml; $P < 0.01$). Changes in circulating plasma NE values were not significantly affected. However, an almost total block of the sympathetic response to SNP-induced hypotension was found after 20 μg/kg of clonidine (i.e., 1 + 4 + 15); mean EPI and NE responses were attenuated by 99% ($P < 0.01$) (Table 1, Fig. 1).

Parallel with the decrease in catecholamine response, clonidine also produced a significant reduction in the hypotensive dose of SNP required (Table 1). Administration of a total dose of 5 μg/kg clonidine decreased the mean SNP requirement by 47% ($P < 0.05$) and 20 μg/kg clonidine by 81% ($P < 0.001$). The catecholamine reductions paralleled the observed decrease in SNP requirement. The effect of different doses of clonidine on the amount of SNP required to

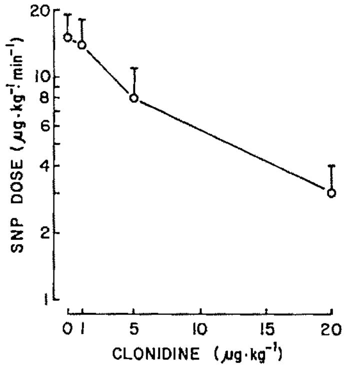

Figure 2. Dose–response relationship between clonidine dose and required dose of sodium nitroprusside to induce 40% hypotension. Sodium nitroprusside requirement is plotted on a log scale. Values shown are the mean ± SEM.

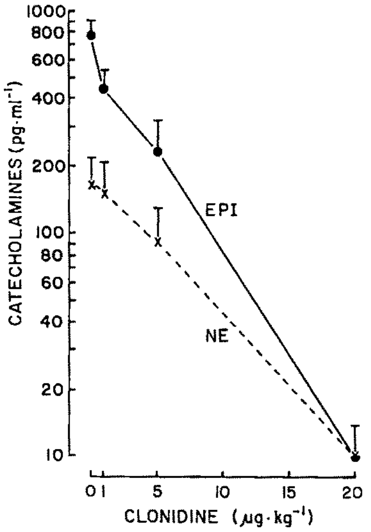

Figure 3. Dose relationship between clonidine and norepinephrine and epinephrine release (plasma level at 30 min minus plasma level at control) in response to induced hypotension. Catecholamine concentrations are plotted on a log scale. Values shown are the mean ± SEM.

induce hypotension is depicted in Figure 2. Figure 3 demonstrates the relationship between clonidine dose and reduction in the 30-min catecholamine response to SNP-induced hypotension. Table 1 summarizes the mean and standard error values for mean arterial pressure, heart rate, norepinephrine, and epinephrine, as well as sodium nitroprusside dose.

Discussion

Supplementation of the antihypertensive action of SNP is almost standard practice and should obviate the need for potentially toxic doses to control blood pressure. During anesthesia, halothane is frequently used for this purpose. Increased concentration of halothane yields deeper levels of anesthesia, thereby decreasing the amount of SNP needed because halothane is a cardiovascular and sympathetic depressant in its own right. However, resorting to an increase in the depth of anesthesia to control blood pressure and heart rate responses can be undesirable in the elderly or in patients with cardiovascular disease.

β-Adrenergic blockade with a drug such as propranolol is another approach to attenuating the β-adrenergic reflex response associated with SNP, and therefore to reducing the required dose. β-Adrenergic blockade reduces the degree to which the heart, through inotropic and chronotropic mechanisms, can compensate for the vasodilatation produced by SNP. β-Blockade may be contraindicated for patients with chronic obstructive pulmonary disease, asthma, or congestive heart failure.

Clonidine attenuates the release of catecholamines by reducing central sympathetic outflow. This reduction is believed to be through a central mechanism (18). Unlike propranolol, clonidine does not block the postsynaptic adrenergic receptors. Yet like propranolol, clonidine significantly reduces the amount of SNP required to produce the desired hypotension, as seen in the present study.

In the present study, sympathetic tone (as indicated by plasma catecholamine levels) (19) varied among the animals during isoflurane anesthesia at 1 MAC. Yet within 5 min of the first period of SNP-induced hypotension, a marked discharge of NE and EPI was seen in each animal lasting the entire 30-min period (Table 1 and Fig. 1). Epinephrine was preferentially released when blood pressure was decreased. This finding is similar to that of Malmejac (20). Observed peak response of NE was at 5 min, whereas EPI levels were still increasing at the 30-min sample point (Fig. 1). When SNP was discontinued, the outpouring of catecholamines subsided over the 30-min recovery time.

In these experiments, three doses of clonidine were used: 1, 4, and 15 µg/kg. Because of clonidine's long duration of action (elimination half-life 20–40 hr) (21), the doses given probably were cumulative and total doses of 5 and 20 µg/kg were achieved. Clonidine is known to reduce circulating levels of EPI and NE (22). In the present experiment no significant decreases in circulating plasma EPI levels occurred during the control periods after clonidine, probably because the initial levels were not elevated in these animals. However, a significant reduction in plasma NE levels did occur (Table 1). Clonidine markedly attenuated the release of catecholamines in a dose-related fasion when the sympathetic nervous system was challenged by SNP-induced hypotension (Fig. 1 and Table 1).

"Primary resistance" to SNP may be mediated by an unusually brisk sympathoadrenal response that occurs as homeostatic mechanisms, especially pressure-sensitive baroreceptor reflexes, attempt to maintain normal arterial pressure. To overcome the increase in homeostatic baroreceptor activity, even greater amounts of SNP are given, and acute tachyphylaxis is observed. No tachyphylaxis was found in the present experiments during the 30-min hypotensive periods. However, catecholamine release seemed to play a large role in SNP dose requirement. A cumulative dose of 20 μg/kg clonidine blocked the SNP hypotension-induced catecholamine release and decreased the required dose of SNP by 81%. Published reports indicate that the decrease in the dose requirement of SNP produced by propranolol was 40% for a similar reduction in MAP (6).

In our animal study, as in human studies (23), clonidine in all doses employed did not significantly alter MAP from that of the control (Table 1). During the normotensive period, plasma levels of NE were reduced only after administration of clonidine. This result was probably due to the anesthesia and lack of surgical stimulation, such that control catecholamine levels were the same as expected in resting supine subjects (EPI 70 pg/ml, NE 171 pg/ml). If higher sympathetic tone had been present initially, a reduction in sympathetic tone, and therefore in circulating catecholamines, would have been predicted. In this light, it should be pointed out that in a situation where blood pressure is dependent on high sympathetic tone, clonidine would be likely to decrease blood pressure.

Attenuation of sympathetic response paralleled decreased doses of SNP required to produce the desired hypotension (Fig. 3). One μg/kg of clonidine had no significant effect on SNP dose, but 5 μg/kg and 20 μg/kg significantly reduced mean SNP requirement by 45% and 81%, respectively. Thus the dose reduction paralleled the reduction in catecholamine release. Dose–response relationships depicted in Figures 2 and 3 suggest that an optimal dose of clonidine can be chosen to reduce the SNP dose while maintaining some degree of sympathetic reactivity. This balance is desirable because it allows for circulatory adjustments to buffer changes, especially during emergency conditions. This interaction between a centrally-acting drug and a peripheral vasodilator has not been reported previously.

In an earlier study, 20 μg/kg of clonidine increased the anesthetic potency of halothane (a reduction of MAC) in dogs by 48% (24). Although we have not measured the effect of clonidine on the potency of isoflurane, perhaps an increase in depth of anesthesia may account in part for some of the significant reduction in SNP dose and catecholamine secretion found in this experiment. Animals in the present study were deliberately maintained on 1 MAC isoflurane rather than halothane. Isoflurane has less myocardial depressant effects than halothane, and probably depresses parasympathetic tone more than sympathetic tone (25,26). In addition, a decrease in catecholamine concentrations has not been found in unstimulated dogs anesthetized with isoflurane (27). Maintenance of sympathetic tone with isoflurane anesthesia reduces the variable effect this factor can have on changes in anesthetic depth. It is therefore more difficult to correlate a reduction in halothane MAC by clonidine to the effect of clonidine on SNP dose reduction in dogs anesthetized with isoflurane, though some potentiation might occur.

Clinical implications of this experiment are limited by the following important factors: 1) During the experimental period, the animals were not subjected to any surgical stimulation or stress. The catecholamine release likely to occur during stimulation or stress may well change the observed log-linear reduction in EPI and NE outflow by the three clonidine doses used. 2) Chronically administered clonidine used either alone or as part of a patient's antihypertensive therapy may not yield the same reduction in catecholamine outflow and SNP dose as in the present experiments where clonidine was used acutely. 3) In this study, 0.02 mg/kg of atropine was administered every hour to prevent clonidine-induced bradycardia. This was done in an attempt to separate sympathetic and parasympathetic components. With increasing doses of clonidine without atropine one could expect a further decrease in heart rate and less of an increase in heart rate during SNP-induced hypotension, both caused by clonidine-increased vagal tone.

However, on the basis of the present data, clonidine may be beneficial in decreasing SNP dose during induced hypotension while leaving sympathetic reserves for unexpected occurrences of hypotension, hypovolemia, or hemorrhage without blocking postsynaptic adrenergic receptors.

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Influence of Moderate Hypothermia on Posterior Tibial Nerve Somatosensory Evoked Potentials

Aart T. van Rheineck Leyssius, MD, Cor J. Kalkman, MD, and James G. Bovill, MD, FFARCSI

VAN RHEINECK LEYSSIUS AT, KALKMAN CJ, BOVILL JG. Influence of moderate hypothermia on posterior tibial nerve somatosensory evoked potentials. Anesth Analg 1986;65:475–80.

Posterior tibial nerve somatosensory evoked potentials (PTN-SSEP) were recorded in eight patients during cardiac surgery with cardiopulmonary bypass and moderate hypothermia (25–28°C). There was no correlation between changes in amplitude and temperature; however, latencies of potentials recorded over the tibial nerve in the popliteal fossa, the lumbar spinal cord, and the cortex increased linearly as temperature decreased. Latency changes correlated well with nasopharyngeal temperature, but only poorly with rectal and lower limb muscle temperatures. During perioperative monitoring of spinal cord function by means of PTN-SSEP, an increase of the first positive cortical peak (P1) greater than 3 msec is considered an indication for intervention. In this study P1 prolonged 1.15 msec/°C ($r = 0.89$, $P < 0.001$). This implies that a temperature decrease of 2–3°C may prolong P1 latency by more than 3 msec.

Key Words: BRAIN—evoked potentials. HYPOTHERMIA—evoked potentials.

Somatosensory evoked potentials after posterior tibial nerve stimulation (PTN-SSEPs) are frequently used for intraoperative monitoring of spinal cord function during procedures such as repair of scoliosis or resection of aneurysms of the thoracic aorta (1,2). During these operations, there is a risk of spinal cord damage because of either excessive traction or interruption of blood supply that will result in postoperative paraplegia if not detected and corrective measures speedily taken. However, other factors associated with surgery, including anesthetic drugs and changes in acid–base status and temperature, can significantly alter evoked potentials and must be taken into account in the interpretation of evoked potentials during surgery.

Hypothermia decreases conduction velocity of impulses along nerve axons and increases synaptic transmission delay due to impaired transmitter release (3–7), thereby prolonging latency of cortical potentials. This has been confirmed in humans for auditory (8,9) and visual stimulation (8,10). The influence of hypothermia on median nerve somatosensory evoked potentials has been studied during surface cooling (11) and during cardiopulmonary bypass (CPB) (8). The latencies of both short and long latency components increased linearly with decreasing temperature. The amplitude of the long latency cortical responses also decreased with hypothermia (8).

Because of the long peripheral pathway involved in PTN-SSEPs, one would expect these latencies to be very sensitive to changes in both peripheral and core temperatures. The purpose of the study presented here was to investigate the effects of hypothermia during CPB on PTN-SSEPs, to determine whether this form of monitoring remains reliable during hypothermia, and to evaluate the relationship between changes in either latency or amplitude and changes in temperature.

Methods

Eight patients undergoing elective cardiac surgery involving CPB with hypothermia were studied. Each patient gave informed consent to participate in the institutionally approved protocol. None had evidence of neurologic or endocrine disease. Demographic details of the patients and the types of operation performed are shown in Table 1.

All patients received lorazepam, 3–5 mg, orally 2 hr before surgery as premedication. Anesthesia was induced with fentanyl, 75 μg/kg, and pancuronium, 0.1 mg/kg, was given for muscle relaxation. After intubation of the trachea the lungs were ventilated with

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Address correspondence to Dr. van Rheineck Leyssius, Department of Anesthesiology, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

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Table 1. Demographic Details of Patients and Types of Operation

Patient	Sex	Age (yr)	Weight (kg)	Height (cm)	Operation
1	F	64	82	170	Mitral valve prosthesis
2	M	44	72	182	Mitral valve prosthesis
3	M	64	74	169	Aortic valve prosthesis
4	F	46	54	170	Mitral valve prosthesis
5	F	45	60	170	Closure of atrial septal defect
6	M	52	84	185	Aortic and mitral valve prosthesis
7	F	50	67	167	Mitral valve prosthesis
8	F	60	74	163	Mitral valve prosthesis
Mean		53	70.9	172	

oxygen/air ($F_{I_{O_2}}$ 0.5) and ventilation adjusted to maintain Pa_{CO_2} between 35 and 40 mm Hg. Additional fentanyl, 25 μg/kg, was given before skin incision. Arterial blood pressure, pulmonary arterial pressure, and the electrocardiogram were monitored with a HP-78534A monitor.

Nasopharyngeal (NPT), rectal (RT), and lower limb muscle (MT) temperatures were measured with an Ellab-100 thermometer connected to temperature probes. The tip of the nasopharyngeal probe was positioned just above the soft palate. The tip of the rectal probe was positioned 5 cm from the anal sphincter. A needle probe was inserted into the lateral head of the gastrocnemius muscle. The thermometer and temperature probes were regularly calibrated against a precision mercury thermometer and gave a linear response between 20 and 40°C, with an accuracy of ±0.1°C.

Output signals from the HP-78534A monitor and the Ellab-100 thermometer were interfaced with a microcomputer, which recorded temperatures and mean arterial blood pressure every 20 sec and stored them, together with time, on a floppy disc. Cardiopulmonary bypass was performed using a Spiroflo-10S bubble oxygenator (Bos–Bentley) with flows of 50 $ml·kg^{-1}·min^{-1}$. Moderate hypothermia (NPT 25–28°C) and hemodilution to a hematocrit of 0.20–0.25 was used. Perfusion pressure was maintained between 40 and 70 mm Hg. If necessary metaraminol or sodium nitroprusside were administered to keep perfusion pressure between these limits. Pa_{CO_2} was maintained between 35 and 45 mm Hg.

A Pathfinder II system was used for nerve stimulation and acquisition of evoked potentials (Nicolet Biomedical Instruments, Madison, WI). Before induction of anesthesia, the posterior tibial nerves at the right and left ankles were identified with a stimulator probe. Subdermal needle electrodes were inserted 2 cm apart at right angles to the axis of the nerves and the motor threshold determined.

Teflon-coated subdermal recording needles were inserted as follows:

1. Right popliteal fossa over the tibial nerve with a reference electrode 4 cm proximal.
2. Over the T12–L1 interspace with a reference electrode over the right iliac crest for lumbar spinal cord recordings.
3. On the scalp at C_z' with a reference electrode at F_{pz} (international 10–20 system).
4. A ground electrode over the right mastoid process.

The impedance of all electrodes was less than 6 kΩ. Evoked potentials were not recorded before induction of anesthesia.

After induction of anesthesia and intubation of the trachea, evoked potentials were acquired by simultaneous stimulation of both posterior tibial nerves with constant current square wave pulses of 200-μsec duration at a frequency of 5.2 pulses/sec. Stimulus intensity was 20 mA, which was supramaximal.

The recorded signal was amplified 50,000 times and filtered between 5 and 250 Hz (−3 dB). An automated protocol was used that continuously recorded averages from the three sites and stored them, together with the start and finish times of each average, on a Winchester disc for later analysis. High-voltage artifacts were automatically rejected by the computer. The analysis time was 130 msec for tibial nerve and cortical recordings. A second digitizer with an analysis time of 100 msec was used for the lumbar recordings because these were often contaminated with ECG artifact, which slowed the speed of acquisition. The average from 128 stimuli was used for each response.

The peak latencies of the negative deflection in the tibial nerve and lumbar responses and of the first positive peak (P1), the first negative peak (N1) and the second positive peak (P2) on the scalp, and the P1–N1 amplitude were measured using on-screen cursors. Both individual patient and pooled data were

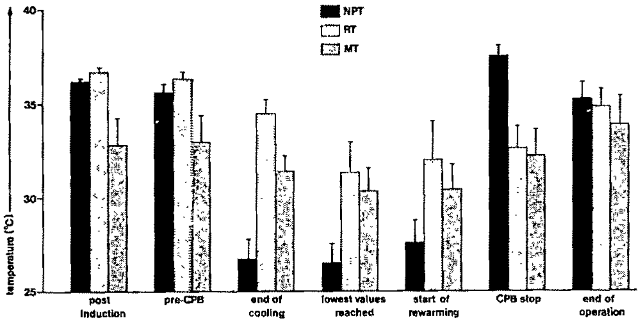

Figure 1. Temperature (mean ± SD) before, during, and after cardiopulmonary bypass (CPB). NPT, nasopharyngeal temperature; RT, rectal temperature; MT, lower limb muscle temperature.

analyzed by linear regression analysis. In order to eliminate the effects of interpatient variability, changes in latency and amplitude from the postinduction values were used for regression analysis. The paired Student's *t*-test was used to test the significance of the differences between means. All results are reported as mean ± SD.

Results

The average duration of CPB was 63 min (range 30–112 min). Nasopharyngeal temperature decreased from 35.6 ± 0.46°C before bypass to 26.7 ± 1.07°C over 8–15 min, with an average rate of cooling of 1.0 ± 0.17°C/min. In all patients, changes in RT and MT lagged behind NPT and often had not reached a steady state when rewarming was started. Rectal temperature decreased from 36.3 ± 0.41°C before bypass to a minimum of 31.3 ± 1.63°C, which often was reached only when NPT had returned to prebypass values. Lower limb muscle temperature decreased from 33.3 ± 1.42°C before bypass to a minimum of 30.3 ± 1.23°C, with a shorter time lag than RT. Average temperatures at various times during surgery are shown in Figure 1.

Satisfactory cortical and tibial nerve evoked potentials were obtained throughout the procedure in all patients, but adequate lumbar potentials could be recorded during CBP in only seven patients. After CPB, satisfactory lumbar recordings could not be acquired in four patients due to pacemaker interference. Typical cortical and lumbar responses from one patient are shown in Figure 2. All latencies increased during hypothermia. Changes in temperatures, latencies, and P1–N1 amplitude from the same patient are shown in Figure 3. Mean absolute latencies and P1–N1 amplitudes before CPB, at 28°C during cooling, at 28°C during rewarming, and at 35.5°C after bypass are given in Table 2.

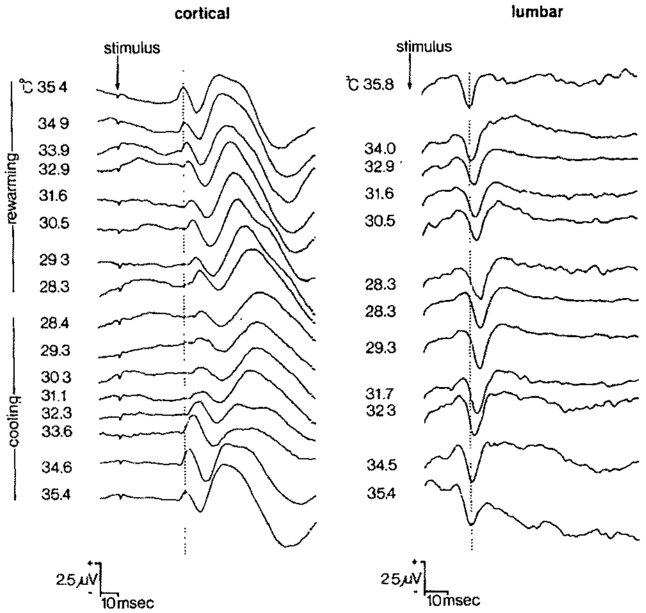

Figure 2. Posterior tibial nerve somatosensory evoked potentials from one patient at different temperatures during cardiopulmonary bypass. Left: cortical responses. Right: lumbar spinal cord responses.

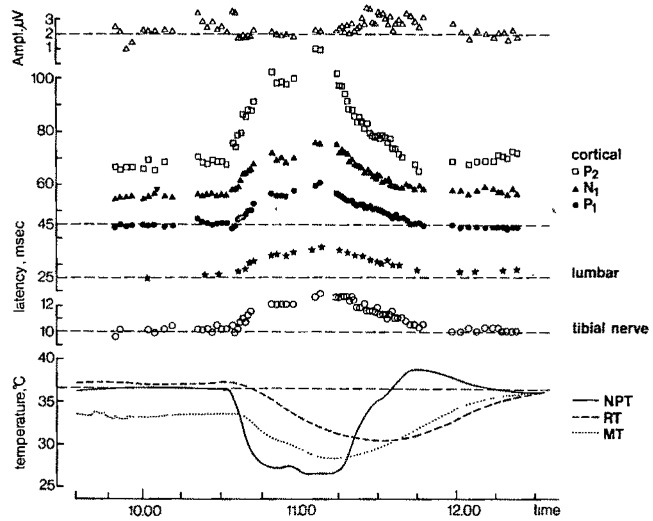

Figure 3. Changes in temperatures, cortical, lumbar, and tibial nerve latencies and P1–N1 amplitude before, during, and after cardiopulmonary bypass in one patient. Abbreviations: NPT, nasopharyngeal temperature; RT, rectal temperature; MT, lower limb muscle temperature; P1, first positive cortical peak; N1, first negative cortical peak; P2, second positive cortical peak. Horizontal dashed line indicates postinduction values.

Cortical latencies in individual patients were always highly correlated with NPT during both cooling and rewarming, with correlation coefficients >0.9. The mean slope of the lines of best fit from the individual patients was for the P1 latency, −1.14 msec/°C (95% confidence interval (CI) −0.80 to −1.49), and for the

Table 2. Latencies and Amplitudes of PTN-SSEPs before, during, and after Cardiopulmonary Bypass

	Prebypass	Cooling (28°C)	Rewarming (28°C)	Postbypass
Tibial nerve latency (msec)	11.1 ± 0.96	12.5 ± 0.77	12.9 ± 1.28	11.1 ± 1.40
Lumbar latency (msec)	27.3 ± 1.80	31.7 ± 0.86	33.2 ± 1.97	—
P1 latency (msec)	46.1 ± 3.34	55.3 ± 3.12	56.4 ± 3.87	46.9 ± 4.40
N1 latency (msec)	55.8 ± 3.76	69.7 ± 3.30	69.8 ± 4.26	56.2 ± 4.41
P2 latency (msec)	68.3 ± 4.87	94.7 ± 7.87	91.4 ± 6.31	70.0 ± 4.45
P1–N1 amplitude (μV)	1.7 ± 0.77	1.2 ± 0.63	1.4 ± 0.73	1.8 ± 0.83

Values are mean ± SD.

Abbreviations: PTN-SSEP, posterior tibial nerve somatosensory evoked potentials; P1, first positive cortical peak; N1, first negative cortical peak; P2, second positive cortical peak.

N1 latency, −1.65 msec/°C (95% CI −1.07 to −2.23). The slope calculated from pooled data from all patients was −1.15 msec/°C for the P1 latency and −1.64 msec/°C for the N1 latency. Scattergrams of pooled data and lines of best fit of changes in tibial nerve, lumbar, and cortical P1 and P2 latencies against NPT are shown in Figure 4.

Tibial nerve and lumbar latencies increased immediately after the start of CPB and correlated highly with NPT during cooling. However, the correlation was less during rewarming (Table 3). Correlation was poor ($r < 0.6$) between all latencies and RT and MT.

Intrapatient variability of P1–N1 amplitude was large, with no correlation between amplitude and temperature. Mean arterial pressure, whether before, during, or after CPB, did not correlate with latency or amplitude at any recording site.

Discussion

Cortical PTN-SSEPs are widely used for intraoperative monitoring of spinal cord function. However, the latencies of these potentials are the sum of the conduction time in the peripheral nerve, spinal cord transit time, and central conduction time, and are therefore less specific for monitoring spinal cord function than are PTN-SSEPs recorded directly from the spinal cord. Ideally, one should measure spinal cord conduction time only, by recording PTN-SSEPs from above and below the potential site of damage, e.g., lumbar and cervical recordings. However, because of a very low signal/noise ratio, satisfactory thoracic and cervical-cord PTN-SSEPs cannot be recorded easily in the operating room from surface electrodes, and electrodes should be placed in the epidural space (12). Satisfactory lumbar spinal cord SSEPs can be recorded from surface electrodes. The large negative deflection and the waveform recorded over the T12–L1 interspace is thought to be closely related to the entry of the afferent volley in the spinal cord (13).

Cortical SSEPs are influenced by anesthetic drugs and temperature changes. Anesthetic techniques suitable for intraoperative spinal cord monitoring should not affect latencies or amplitudes once anesthesia is stabilized. Somatosensory evoked potential latencies are increased by isoflurane and enflurane (14). Nitrous oxide diminishes median nerve SSEP amplitudes without affecting latencies (14,15). High-dose fentanyl anesthesia is an accepted technique for open heart surgery (16). With this technique volatile agents and nitrous oxide can be avoided. Low doses of fentanyl alter PTN-SSEPs when compared with preoperative waking values (17). The influence of high doses of opioids on PTN-SSEPs has not yet been reported.

In this study we were able to record reproducible PTN-SSEPs of high quality before, during, and after CPB. Latencies were stable in the period from induction of anesthesia to the start of CPB. At the end of the operation, when temperatures had returned to prebypass values, latencies were not significantly different from prebypass values (Table 2).

A linear correlation, occurring during CPB, between NPT and both short and long latency median nerve SSEPs has been described; although very variable, amplitudes generally declined with decreasing temperature (8). The central conduction time for median nerve evoked potentials, defined as the N13–N20 interpeak latency, has been shown to increase exponentially with decreasing esophageal temperature (18). We found a linear correlation between PTN-SSEP latencies and temperature, but no correlation between amplitude changes and temperature. During cooling, latencies from the three recording sites were highly correlated with NPT. In the steady state, NPT is a good estimator of the temperature of mixed venous blood and highly perfused organs such as the brain. However, during rapid temperature changes seen during CPB, NPT lags behind mixed venous blood temperature (19).

Lower limb muscle temperature was used as an estimator of tibial nerve temperature. We had expected that the increase in tibial nerve and lumbar spinal cord latencies would have better correlated with MT than with NPT. However, these latencies in-

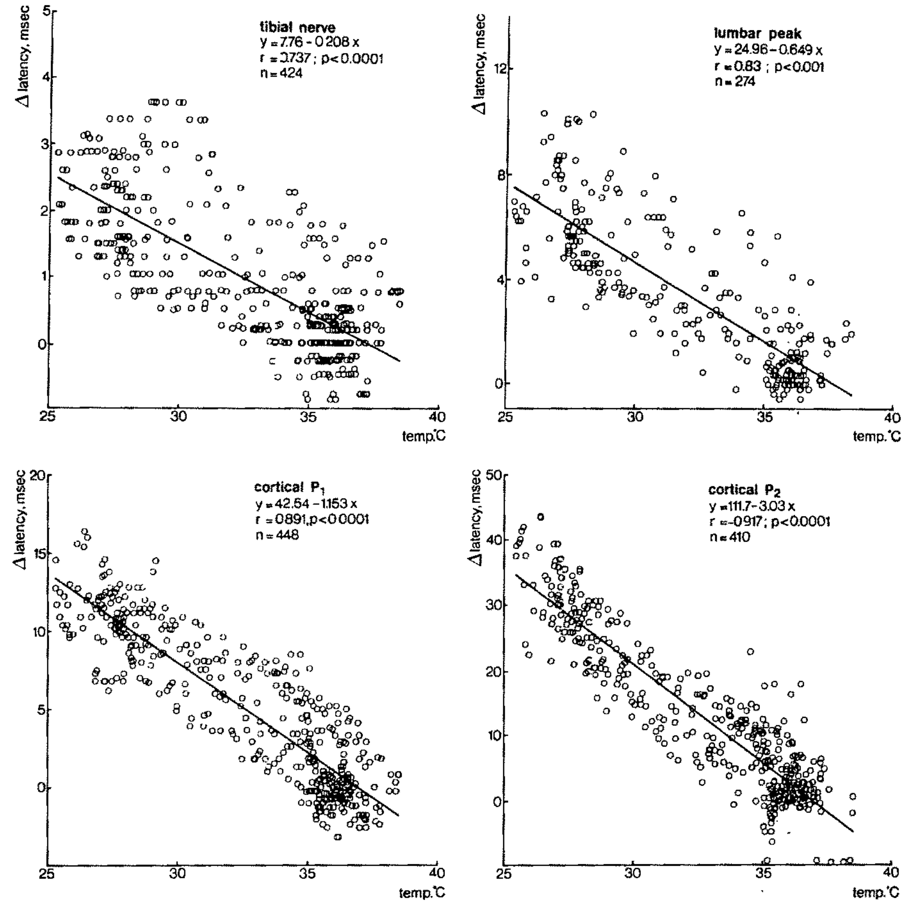

Figure 4. Scattergrams of pooled data and lines of best fit of changes in latency from postinduction values (Δ latency) vs nasopharyngeal temperature during cardiopulmonary bypass.

creased immediately after the start of CPB, before MT had decreased. In four patients, NPT remained at steady state during CPB for longer than 30 min, whereas RT and MT continued to decrease. This continuing peripheral cooling was reflected by further increases in tibial nerve and lumbar latencies. The temperature of the peripheral nerve would therefore appear to be determined by both muscle temperature and the temperature of the blood perfusing the limb. At the start of cooling, tibial nerve temperature decreases initially parallel to NPT rather than MT. This is presumably due to the close anatomical association of nerve and femoral/popliteal artery. During rewarming, cortical latencies were highly correlated with NPT. However, there was a lower correlation between tibial nerve and lumbar latencies and any temperature. During the early phase of rewarming, when NPT was increasing, MT was still decreasing and was obviously influencing nerve temperature and thus nerve conduction velocity. The latency prolongation of the cortical peaks is also the result of an increase in synaptic delay in the central nervous system. This is clearly demonstrated by the large increase in the P2 latency in relation to the P1 latency (Table 2, Fig. 3).

The relationship between latency and temperature has important implications for monitoring spinal cord function with PTN-SSEPs. During CPB under moderate hypothermia, a stable response suitable for quantitative monitoring of latencies can be achieved only when no temperature gradients exist between peripheral and central tissues. In this study, CPB lasted less than 2 hr, and equilibrium was not reached. Because cortical peaks of PTN-SSEPs remained of high quality during moderate hypothermia, disappearance of the PTN-SSEPs or sudden gross latency prolongations may be used as an indication of impending damage to the spinal cord. When monitoring spinal cord function during procedures without CPB, e.g., scoliosis surgery, an intraoperative latency increase of more than 3 msec for the first positive cortical peak or a more than 50% decrease in P1–N1 amplitude is considered an indication for intervention (1). A decrease in NPT of 2–3°C can prolong P1 latency by more than 3 msec. In this study, temperature changes were induced by central cooling or heating, and peripheral tissue temperature lagged behind central temperature. This damped the temperature response of PTN-SSEPs. Inadvertent cooling during prolonged surgery

Table 3. Regression Coefficients from Pooled Data of Latencies and Amplitudes of PTN-SSEPs against Nasopharyngeal Temperature during Cardiopulmonary Bypass

	Cooling			Rewarming			Cooling plus Rewarming		
	Slope[a]	*r*	*n*	Slope[a]	*r*	*n*	Slope[a]	*r*	*n*
Tibial nerve latency	−0.21	0.87	206	−0.21	0.62	151	−0.21	0.73	424
Lumbar latency	−0.73	0.91	158	−0.52	0.64	79	−0.65	0.83	274
P1 latency	−1.23	0.94	211	−1.05	0.85	163	−1.15	0.89	448
N1 latency	−1.80	0.94	212	−1.40	0.86	166	−1.64	0.90	452
P2 latency	−3.54	0.96	190	−2.27	0.82	149	−3.03	0.92	410
P1–N1 amplitude	0.09	0.47	204	0.11	0.35	162	0.07	0.29	435

Abbreviations: PTN-SSEP, posterior tibial nerve somatosensory evoked potentials; *r*, correlation coefficient; *n*, number of observations; P1, first positive cortical peak; N1, first negative cortical peak; P2, second positive cortical peak.

[a] Latency slopes are msec/°C, amplitude slope is μV/°C.

without CPB is a slow process in which gradients will be minimal. We hypothesize that latency increase/°C will be even greater in these operatioins than observed in this study. Any slowing of conduction in the peripheral nerve will be reflected in the cortical latencies. In these circumstances tibial nerve and lumbar spinal cord SSEPs may give useful information on peripheral conduction delay. Correction should be made for observed latencies for the decrease in nasopharyngeal temperature.

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The Effect of Cimetidine on Anesthetic Metabolism and Toxicity

Margaret Wood, MBChB, FFARCS, Jack Uetrecht, MD, PhD, James M. Phythyon, MD, Sheila Shay, BS, Brian J. Sweetman, PhD, Omar Shaheen, MD, PhD, and Alastair J. J. Wood, MBChB, MRCP

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Because the H_2-receptor antagonist cimetidine has been shown to inhibit drug metabolism, the effects of cimetidine on anesthetic metabolism and toxicity were investigated in a rat model. Cimetidine decreased inorganic plasma fluoride production after methoxyflurane administration both in 21% oxygen ($P < 0.001$) and in 100% oxygen ($P < 0.001$). Phenobarbital produces an increased fluoride formation after methoxyflurane anesthesia, and this flouride formation is also reduced by cimetidine ($P < 0.005$). There was no significant difference between the plasma fluoride levels in rats anesthetized with halothane or enflurane. Although cimetidine inhibited the in vivo defluorination of methoxyflurane, fluoride levels were still within the nephrotoxic range, and cimetidine is not likely to play a role as part of a preanesthetic regimen that would permit the increased clinical use of methoxyflurane. Cimetidine also inhibited the oxidative metabolism of halothane; cimetidine decreased ($P < 0.05$) trifluoroacetic acid concentrations after halothane anesthesia in 21% oxygen and in 100% oxygen and decreased ($P < 0.05$) bromide concentrations after halothane anesthesia in 100% oxygen. Trifluoroacetic acid levels were less ($P < 0.02$) after halothane anesthesia in 14% oxygen as compared with 100% oxygen, indicating a reduction in oxidative metabolism under hypoxic conditions. However, bromide concentrations were maximal after halothane anesthesia in 21% oxygen, and significantly ($P < 0.001$) less after halothane anesthesia in 14% and 100% oxygen. Bromide production, therefore, seems to be inhibited by both hypoxia and hyperoxia. Cimetidine decreased ($P < 0.001$) the severity of liver damage as assessed by histologic grading in the hypoxia–enzyme induced rat model of halothane hepatotoxicity but had no effect in the triiodothyronine-model of halothane hepatotoxicity. Thus cimetidine appears to afford partial protection against halothane-induced hepatic necrosis in the phenobarbital–hypoxia rat model.

Key Words: ANESTHETICS, INHALATION—halothane, enflurane, methoxyflurane. BIOTRANSFORMATION—metabolites, cimetidine. LIVER—hepatotoxicity, metabolism. PHARMACOLOGY—cimetidine.

The histamine H_2-receptor antagonist cimetidine, through binding of its imidazole group to cytochrome P-450, has been shown to inhibit the metabolism of a number of drugs (1,2,3). Cimetidine is now widely prescribed for a large number of surgical patients for both anesthetic and nonanesthetic related indications, and the possibility exists for interaction between cimetidine and the inhalation anesthetic agents.

It is well-recognized that halothane-induced hepatic necrosis occurs when rats are pretreated with phenobarbital to produce enzyme induction and are then anesthetized with halothane under hypoxic conditions (phenobarbital–hypoxia model) (4,5). During normal oxygen conditions, halothane is metabolized via an oxidative pathway to trifluoroacetic acid (TFA) and bromide, whereas hypoxic conditions promote increased metabolism via a reductive route to fluoride, the exhaled metabolites, 2-chloro-1,1,1-trifluoroethane (CTE) and 2 chloro-1,1-difluoroethylene (CDE) and to bromide. Both these pathways are P-450-dependent. Therefore, cimetidine might inhibit the metabolism of halothane by the oxidative and reductive pathways, the relative contributions of which would depend on the ambient oxygen concentration. The metabolism of halothane by the reductive pathway to reactive intermediates is thought to be a mechanism in the etiology of halothane hepatotoxicity. Because

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Address correspondence to Dr. Wood, Department of Anesthesiology, Vanderbilt University, Nashville, TN 37232.

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cimetidine is a potent inhibitor of hepatic drug metabolism, we postulated that cimetidine might protect against halothane-induced hepatotoxicity.

We have previously developed an animal model in which rats, pretreated with triiodothyronine (T_3), develop hepatic necrosis after halothane anesthesia at normal (21%) oxygen concentration (T_3 model) (6). The phenobarbital–hypoxia and T_3 models of halothane hepatotoxicity exhibit fundamental differences: hypoxia is required for the phenobarbital–hypoxia model but not for the T_3 model, hepatic necrosis correlates with the reductive pathway to liberate fluoride in the phenobarbital–hypoxia model but not in the T_3 model, and starvation and feeding have important but opposite effects on the degree of toxicity in the two models (7). Therefore the potential exists for cimetidine to have a different effect on toxicity in the two models.

The fluorinated ethers, methoxyflurane and enflurane, are metabolized by an oxidative route to several metabolites, one of which is inorganic fluoride ion (8,9). Inorganic fluoride has been shown to be responsible for the acute polyuric renal lesion that occurs after methoxyflurane administration (10). Enzyme induction with phenobarbital increases the metabolism and production of fluoride from methoxyflurane in rats and causes a parallel increase in nephrotoxicity (10,11). However, after enflurane anesthesia no increase in fluoride production occurs in phenobarbital-pretreated rats (12), although enzyme induction increases in vitro fluoride liberation in isolated liver microsomes (8). In contrast, halothane undergoes minimal defluorination under normal oxygen concentrations.

The purpose of the present study was threefold: first, to determine the effect of cimetidine on the defluorination of the inhalation anesthetic agents, methoxyflurane, halothane, and enflurane; second, to determine the effects of cimetidine on the oxidative and reductive metabolism of halothane using the production of TFA as a probe of oxidative metabolism and fluoride production as an index of reductive metabolism; and third, to investigate the effect of cimetidine on halothane hepatotoxicity and halothane metabolism in both the phenobarbital–hypoxia and T_3 models of halothane hepatotoxicity.

Methods

Effect of Cimetidine on Anesthetic Defluorination

A series of experiments were conducted to determine the effect of cimetidine on the defluorination of methoxyflurane, enflurane and halothane. Groups of male Fischer 344 rats (100–125 g) received either cimetidine, 180 mg/kg intraperitoneally, or saline 60 min before anesthesia. Groups of six to eight animals were then anesthetized in an airtight plexiglass chamber for 2 hr with either 1.8% enflurane in 21% oxygen, 0.25% methoxyflurane in 21% oxygen, or 0.25% methoxyflurane in 100% oxygen. Other groups of male Fischer 344 rats received phenobarbital, 75 mg/kg intraperitoneally, for 5 days and on the sixth day received either cimetidine, 180 mg/kg intraperitoneally, or saline 60 min before anesthesia. These rats were then anesthetized with 0.25% methoxyflurane in 21% oxygen for 2 hr. Groups of male Sprague–Dawley rats received either cimetidine, 180 mg/kg intraperitoneally, or saline 60 min prior to anesthesia with 1% halothane in 14% oxygen for 2 hr. All the rats were killed immediately after anesthesia, and estimations of plasma inorganic fluoride were carried out using an Orion fluoride ion electrode (Orion Research, Cambridge MA).

Effect of Cimetidine on the Oxidative Metabolism of Halothane

During normal ambient oxygen conditions, halothane is metabolized via the oxidative pathway to TFA and bromide, whereas enzyme induction and hypoxic conditions promote metabolism via the reductive route to fluoride, bromide, and the exhaled volatile metabolites, CTE and CDE. Thus the purpose of the second group of experiments was to determine the effect of cimetidine on the oxidative metabolism of halothane under varying conditions of oxygenation.

Groups of male Sprague–Dawley rats (100–125 g) received either saline or cimetidine (180 mg/kg intraperitoneally) 60 min prior to anesthesia. Groups of 6–8 animals were than anesthetized in an airtight plexiglass chamber for 2 hr with 1% halothane in 14,21, or 100% oxygen. After anesthesia, the rats received further doses of cimetidine (180 mg/kg intraperitoneally) or saline 1 hr and 5 hr after anesthesia. The rats received further doses of cimetidine during the postanesthetic period because preliminary experiments had shown that mean cimetidine concentrations after a single dose of cimetidine (180 mg/kg intraperitoneally) were 3.5 ± 0.43 μg/ml and 0.3 ± 0.06 μg/ml 1 and 2 hr after injection, respectively, indicating that cimetidine levels were below the therapeutic range 2 hr after administration. All the rats were killed 8 hr after anesthesia, and blood samples were taken for the determination of TFA and bromide concentrations.

Plasma TFA and bromide concentrations were determined by gas-chromatographic mass spectrometric analysis after methylation with dimethylsulfate, using a modification of the method described by Maiorino et al. (13). An LKB-9000 GC/MS system coupled to a PDP-12A computer was used. The system had been modified so that selected ion monitoring software could control the accelerating voltage (~3 kV) via a Kepco programmable power supply. The ion source temperature was maintained at 200°C, ionization energy at 70 eV for electron impact ionization, and trap current at 60 μA. Using a gas tight syringe, headspace samples (500 μl) were injected onto a packed glass column, 2-mm inner diameter, 6-m length, containing Carbowax 400 on Porasil. Helium carrier gas flow was set to about 20 ml/min. The gas chromatograph was interfaced to the mass spectrometer using the standard, two-stage stainless steel jet separator. For the analysis of bromide, a column temperature of 60°C was used, and the instrument was set to alternately monitor m/z 94 ($CH_3{}^{79}Br^+$) and m/z 96 ($CH_3{}^{81}Br^+$). The ratio of those two ions was used as a means of evaluating instrumental stability. For the analysis of TFA, a column temperature of 110°C was used, and the instrument was set to monitor m/z 59 ($COOCH_3{}^+$). No internal standard was used on either of these assays, which required quantitation to be achieved with a concomitantly obtained standard curve containing ten different concentrations of bromide of TFA as external standards in the range 0.02–4.0 mM. Separate experiments demonstrated intra and interassay variations of less than 5%.

Effect of Cimetidine on Halothane Hepatotoxicity and Metabolism

A third group of experiments was conducted to determine the effect of cimetidine on halothane hepatotoxicity and halothane metabolism in the phenobarbital and T_3 rat models. Groups of male Sprague–Dawley rats (100–125 g) received phenobarbital, 75 mg/kg intraperitoneally, for 5 days and on the sixth day received either cimetidine (180 mg/kg intraperitoneally) or saline 60 min before anesthesia. The animals were then anesthetized in groups of 6–8 in an airtight plexiglass chamber with 1% halothane in 14% oxygen for 2 hr as previously described for the phenobarbital–hypoxia model of halothane hepatotoxicity (6,7). The rats were either killed immediately (for determination of plasma fluoride concentrations) or 24 hr after anesthesia (for determination of plasma serum glutamic pyruvic transaminase concentrations (SGPT) and hepatic histologic grading). Estimations of SGPT concentrations were performed by a quantitative colorimetric method (14) in rats killed 24 hr after anesthesia. The rat livers were removed for histologic grading, which we have previously described (6), by a pathologist who was unaware of the treatment received; a grade of 0 indicated that no lesion was present and a grade of 4+ indicated extensive centrilobular necrosis present throughout the section (6).

Further groups of rats were pretreated with phenobarbital (75 mg/kg intraperitoneally) for 5 days and on the sixth day received either cimetidine (180 mg/kg intraperitoneally) or saline 60 min prior to anesthesia. These rats were then anesthetized for 2 hr with halothane in 14% oxygen. After anesthesia, the rats received further doses of cimetidine (180 mg/kg) or saline 1 and 5 hr after anesthesia. The rats were killed 8 hr after anesthesia, and blood samples were taken for determination of plasma TFA and bromide concentrations as described above.

In order to evaluate the effects of cimetidine on urinary fluoride excretion in the phenobarbital–hypoxia model of halothane hepatotoxicity, further groups of rats were assigned to one of four groups. The rats in group 1 were control rats who received no pretreatment, no cimetidine, and no anesthesia. Rats in group 2 received saline for 5 days, no cimetidine, and on the sixth day they were anesthetized with 1% halothane in 14% oxygen for 2 hr. Rats in group 3 and 4 received phenobarbital, 75 mg/kg, for 5 days and on the sixth day received either cimetidine, 180 mg/kg intraperitoneally, (group 3) or saline (group 4) 60 min before anesthesia. Rats in groups 3 and 4 were anesthetized with 1% halothane in 14% oxygen for 2 hr. The rats in groups 3 and 4 received further doses of cimetidine (group 3) or saline (group 4) 1 and 5 hr after anesthesia. The rats in all groups were placed in metabolic cages immediately after anesthesia and urine was collected for 24 hr for the measurement of urinary fluoride excretion. Inorganic fluoride was measured using the Orion ion-specific electrode.

The effect of cimetidine on halothane hepatic toxicity and metabolism in the T_3 model was determined using groups of male Sprague–Dawley rats (100–125 g) who received 5 $mg{\cdot}kg^{-1}{\cdot}day^{-1}$ of T_3 or the same volume of the vehicle for T_3 injection (intraperitoneally) for 5 days (6,7). On the sixth day, the rats were pretreated with cimetidine (180 mg/kg intraperitoneally) or saline 60 min before anesthesia. The rats were anesthetized for 2 hr with halothane, 1%, in air (21% oxygen concentration). The rats were then killed 4 hr after anesthesia, and blood samples were taken for estimations of SGPT concentrations. The livers were removed for histologic grading as previously described (6). Further groups of rats pretreated with T_3 for 5 days received cimetidine (180 mg/kg intraperitoneally) or saline 60 min before anesthesia. The rats were then anesthetized with 1% halothane in air for 2 hr. After anesthesia, the rats received further doses of cimetidine or saline, 1 and 5 hr after anesthesia. The rats were killed 8 hr after anesthesia and blood samples taken for the determination of plasma TFA and bromide concentrations.

Rats were killed at different times after anesthesia for a number of reasons. Maximal biochemical and histologic damage is observed 4 hr after halothane anesthesia in the T_3 model (6), whereas in the phenobarbital–hypoxia model only minimal damage is seen in the early postanesthetic period (4,5). Therefore, the rats were killed 4 hr after halothane anesthesia when studying the T_3 model and 24 hr after anesthesia when investigating the phenobarbital–hypoxia model. Measurement of plasma fluoride levels was carried out immediately after anesthesia in order to obtain maximum elevation of this parameter (7). Rats were killed 8 hr after anesthesia for determination of TFA and bromide concentrations because preliminary observations had indicated that during the time period 8–12 hr postanesthesia, TFA and bromide concentrations are maximally elevated. These observations are in keeping with the findings of other workers (13).

The results from the three series of experiments were analyzed using Student's *t*-test for unpaired data or the Wilcoxon nonpaired rank sum test when appropriate. $P < 0.05$ was taken as the minimal level of significance.

Results

Effect of Cimetidine on Anesthetic Defluorination

The effects of cimetidine on anesthetic in vivo defluorination are shown in Table 1. Cimetidine significantly ($P < 0.001$) decreased inorganic plasma fluoride levels after methoxyflurane anesthesia under both 21 and 100% oxygen, and in addition, also significantly reduced ($P < 0.005$) the increased fluoride formation produced by phenobarbital pretreatment. However, cimetidine had no significant effect on the plasma fluoride levels in rats that were anesthetized with either halothane or enflurane.

Table 1. The Effect of Cimetidine on Mean Plasma Fluoride Concentrations Immediately after Anesthetic Exposure

Pretreatment and anesthesia	*n*	Fluoride in μm (mean ± SEM)
Saline, methoxyflurane, 21% O_2	25	13.04 ± 0.22
Cimetidine, methoxyflurane, 21% O_2	25	10.92 ± 0.27[a]
Saline, methoxyflurane, 100% O_2	25	13.52 ± 0.25
Cimetidine, methoxyflurane, 100% O_2	26	10.64 ± 0.28[a]
Phenobarbital, saline, methoxyflurane, 21% O_2	26	111.77 ± 2.83
Phenobarbital, cimetidine, methoxyflurane, 21% O_2	25	94.00 ± 4.45[b]
Saline, enflurane, 21% O_2	19	13.46 ± 0.71
Cimetidine, enflurane, 21% O_2	19	12.19 ± 0.53
Saline, halothane, 14% O_2	10	3.61 ± 0.35
Cimetidine, halothane, 14% O_2	9	3.11 ± 0.28
Saline, 14% O_2	23	2.95 ± 0.15
Cimetidine, 14% O_2	25	2.43 ± 0.22

See Methods section for full explanation of medication.

[a] $P < 0.001$, compared with saline-pretreated rats.

[b] $P < 0.005$, compared with saline-pretreated rats.

Effect of Cimetidine on Oxidative Metabolism of Halothane

Table 2 shows the effect of varying oxygen conditions of TFA production from halothane. Production of TFA after halothane anesthesia was not significantly different in 21% oxygen as compared to 100% oxygen, but mean plasma TFA concentrations were significantly less ($P < 0.02$) after halothane anesthesia in 14% oxygen as compared to 100% oxygen, indicating a reduction in oxidative metabolism under hypoxic conditions.

The effect of oxygenation on bromide production from halothane is also shown in Table 2. Mean plasma bromide concentrations were maximal after halothane anesthesia in 21% oxygen, but were significantly less after anesthesia in 14 ($P < 0.001$) and 100% ($P < 0.001$) oxygen when compared to 21% oxygen concentrations. These results imply that bromide production may be inhibited by both hypoxia and hyperoxia.

The effects of cimetidine on the oxidative metabolism of halothane are shown in Table 2. Cimetidine decreased the production of both TFA and bromide from halothane under all conditions, but this decrease reached statistical significance for TFA only after halothane anesthesia in 21 and 100% oxygen and for bromide only during halothane anesthesia in 100% oxygen. These results imply significant inhibition of oxidative metabolism by cimetidine.

The Effect of Cimetidine on Halothane Hepatotoxicity

The effects of cimetidine on halothane hepatotoxicity in the phenobarbital–hypoxia model are shown in Table 3. Cimetidine significantly decreased the histologic severity of the lesion ($P < 0.001$) 24 hr after halothane anesthesia, but the decrease in SGPT concentrations was not significant. Inorganic plasma fluoride levels measured immediately after anesthesia were elevated, in keeping with previous work (7).

Table 2. The Effect of Oxygenation and Cimetidine on Oxidative Halothane Biotransformation

Pretreatment and anesthesia	n	TFA in μM (mean ± SEM)	Bromide in μM (mean ± SEM)
1% Halothane, 14% O_2, no cimetidine	10	437.5 ± 23.6	667.5 ± 58.5
1% Halothane, 14% O_2, cimetidine	10	387.6 ± 21.4	555.0 ± 40.3
1% Halothane, 21% O_2, no cimetidine	10	591.4 ± 31.2[a]	1220.4 ± 70.4
1% Halothane, 21% O_2, cimetidine	10	501.7 ± 24.7	1135.0 ± 107.9
1% Halothane, 100% O_2, no cimetidine	10	542.2 ± 32.1[a]	799.7 ± 48.0[a]
1% Halothane, 100% O_2, cimetidine	10	413.4 ± 52.4	660.9 ± 39.3

See Methods section for full explanation of medication.
Abbreviation: TFA, trifluovoacetic acid.
[a] $P < 0.05$, compared with cimetidine-pretreated rats.

However, there was no significant difference between the mean plasma fluoride levels in phenobarbital-pretreated rats that had received cimetidine ($n = 7$; 15.76 ± 1.33 μM) and phenobarbital-pretreated rats that did not receive cimetidine ($n = 9$; 12.87 ± 0.84 μM). The effect of cimetidine on 24-hr urinary fluoride production in the phenobarbital–hypoxia model is shown in Table 4. There was no significant difference between urinary fluoride production in cimetidine- or noncimetidine-pretreated rats, although the expected increase in fluoride production associated with enzyme induction and halothane anesthesia under hypoxic conditions was observed. Thus we were unable to detect an effect of cimetidine on the reductive metabolism of halothane, as assessed by plasma and urinary fluoride production. Table 5 shows the effect of cimetidine on halothane hepatotoxicity in the T_3 model. Cimetidine had no significant effect on the histologic severity of the lesion or SGPT concentrations in the T_3 model, indicating that cimetidine produced no protection against hepatic necrosis.

The effects of cimetidine on halothane metabolism in both the T_3 and phenobarbital–hypoxia models of hepatotoxicity are shown in Figures 1 and 2. Figure 1 shows first, the effect of T_3 on oxidative halothane metabolism and second, the effect of cimetidine on oxidative halothane metabolism in the T_3 model. Oxidative metabolism was markedly reduced in the T_3 model; mean plasma bromide concentrations were 1220.4 ± 70.4 μM in vehicle-pretreated rats anesthetized with 1% halothane in 21% oxygen for 2 hr compared to 550.0 ± 33.2 μM in rats pretreated with T_3 and anesthetized with 1% halothane in 21% oxygen ($P < 0.001$). Similarly, mean plasma TFA concentrations were significantly ($P < 0.001$) less in T_3-pretreated rats anesthetized with halothane in 21% oxygen (268.7 ± 19.8 μM) than in saline-pretreated rats anesthetized with halothane in 21% oxygen (591.4 ± 31.3 μM). However, there was no significant reduction by cimetidine in mean plasma TFA or bromide concentrations in the T_3 model.

Table 3. The Effect of Cimetidine on Halothane Hepatotoxicity in the Phenobarbital–Hypoxia Model in Rats

Pretreatment and anesthesia	n	Histologic score (mean ± SEM)	SGPT in U/L (mean ± SEM)
Phenobarbital, cimetidine, 1% halothane, 14% O_2	15	0.87 ± 0.15	57.65 ± 3.28
Phenobarbital, saline, 1% halothane, 14% O_2	18	1.78 ± 0.10[a]	60.94 ± 2.78

See Methods section for full explanation of medication.
[a] $P < 0.001$, compared with cimetidine-pretreated rats

Figure 2 shows the effect of cimetidine on halothane metabolism in the phenobarbital–hypoxia model of hepatotoxicity. There was no significant difference in either mean plasma TFA or bromide concentrations in control phenobarbital-pretreated rats (TFA = 1338.0 ± 94.6 μM; bromide = 2320.0 ± 121.2 μM) or cimetidine phenobarbital-pretreated rats (TFA = 1315.0 ± 56.8 μM; bromide = 2720.0 ± 172.5 μM), indicating that cimetidine does not significantly inhibit oxidative halothane metabolism in the phenobarbital–hypoxia model. Phenobarbital pretreatment significantly ($P < 0.001$) increased mean plasma TFA concentrations from 437.5 ± 23.6 to 1338.0 ± 94.6 μM and mean plasma bromide concentrations from 667.5 ± 58.5 to 2320.0 ± 121.2 μM (Fig. 2), indicating that, as expected, phenobarbital enzyme induction increased both oxidative and reductive metabolism.

Discussion

The results presented in this study indicate that cimetidine, an H_2-receptor antagonist that also inhibits drug metabolism, does not inhibit anesthetic defluorination in a manner that might have clinical application. Cimetidine did not significantly inhibit the in vivo defluorination of enflurane or halothane. Although Fischer 344 rats treated with phenobarbital

Table 4. Urinary Inorganic Fluoride Production in the Phenobarbital–Hypoxia Model

Pretreatment and anesthesia	n	Urinary inorganic fluoride in μg/24 hr (mean ± SEM)
Saline, no anesthesia	10	23.82 ± 2.05
Saline, no cimetidine, halothane, 14% O_2	8	27.41 ± 2.02
Phenobarbital, no cimetidine halothane, 14% O_2	10	39.25 ± 3.68
Phenobarbital, cimetidine halothane; 14% O_2	8	37.21 ± 2.89

See Methods section for full explanation of medication.
Rats receiving cimetidine were given cimetidine, 180 mg/kg intraperitoneally 60 min before anesthesia, and 1 and 5 hr after anesthesia.

Table 5. The Effect of Cimetidine on Halothane Hepatotoxicity in the T_3 Model in Rats

Pretreatment and anesthesia	n	Histologic score (mean ± SEM)	SGPT U/L (mean ± SEM)
T_3, no cimetidine, 1% halothane, 21% O_2	7	2.0 ± 0.3	539.8 ± 217.7
T_3, cimetidine, 1% halothane, 21% O_2	5	1.9 ± 0.4	964.3 ± 260.9

See Methods section for full explanation of medication.
Abbreviation: T_3, triiodothyronine.

and cimetidine and then anesthetized with methoxyflurane had statistically significantly lower serum fluoride levels than rats not treated with cimetidine, the levels were still within the nephrotoxic range (10). Thus it appears unlikely that the use of cimetidine as part of an anesthetic regimen would allow safe increased clinical use of methoxyflurane. Clinical studies by Yeager et al. showed no significant difference in serum fluoride levels from patients anesthetized with enflurane after cimetidine administration compared with fluoride levels in patients who did not receive cimetidine (15).

We have demonstrated that cimetidine reduces the oxidative metabolism of halothane, probably through inhibition of cytochrome P-450, and that this is not significant during hypoxic halothane anesthesia when metabolism is shunted toward the reductive pathway. Plummer et al., using serum bromide concentrations as an index of oxidative metabolism, suggested that cimetidine does not inhibit the oxidative metabolism of halothane (16). Bromide is a product of both the oxidative and reductive pathways of halothane metabolism, so that measurement of bromide concentrations does not provide definitive information of the oxidative pathway under all conditions. In addition, Plummer et al. only determined bromide concentrations after halothane anesthesia under hypoxic conditions, which might have obscured alteration in the oxidative pathway, whereas in our studies, bromide concentrations were determined under varying conditions of oxygenation. In addition, in our study serum TFA, which is produced solely from the oxidative pathway, was also used as an index of oxidative metabolism.

We were unable to detect inhibition of reductive metabolism by cimetidine in the hypoxic enzyme-induced Sprague–Dawley rat model of halothane hepatotoxicity, as assessed by both plasma fluoride concentration immediately after anesthesia and cumulative 24-hr urinary fluoride excretion. In contrast, Plummer et al. demonstrated that a smaller dose (120 mg/kg) of cimetidine reduced posthalothane urinary fluoride excretion (16). Not only was our initial dose of cimetidine larger (180 mg/kg), but we also gave two more doses of cimetidine because preliminary experiments showed that the cimetidine level was reduced to 0.3 μg/ml 2 hr after administration of the first dose. Plummer et al. demonstrated that cimetidine inhibited volatile metabolite exhalation (16), which is also thought to be an index of reductive metabolism. Volatile metabolism exhalation may be a more sensitive measure of reductive halothane metabolism than urinary fluoride excretion because not all of the urinary fluoride is derived from halothane metabolism. Furthermore, the more sustained cimetidine concentration produced in our study may inhibit the renal clearance of fluoride because cimetidine has been shown to increase serum creatinine (17). Therefore, although we were unable to demonstrate that cimetidine, 180 mg/kg, inhibited the reductive metabolism of halothane in the phenobarbital–hypoxia model of halothane liver toxicity, the study of Plummer et al. was able to provide evidence that cimetidine, 120 mg/kg, inhibited the reductive metabolism of halothane.

The effect of cimetidine on halothane biotransformation at different inspired oxygen concentrations was interesting. As expected, we demonstrated that hypoxia resulted in reduced oxidative metabolism with consequent decreased TFA production. However, oxidative metabolism appeared to be inhibited by hyperoxia as well. Although the decrease in TFA did not reach statistical significance and the decrease in bromide could be explained by a decrease in the reductive pathway, the reductive pathyway should be an insignificant source of bromide even at 21% oxygen, and together the results suggest that hypoxia inhibits the oxidative metabolism of halothane.

Cimetidine has been shown to protect against acetaminophen hepatotoxicity in mice, presumably because of inhibition of the hepatic microsomal mon-

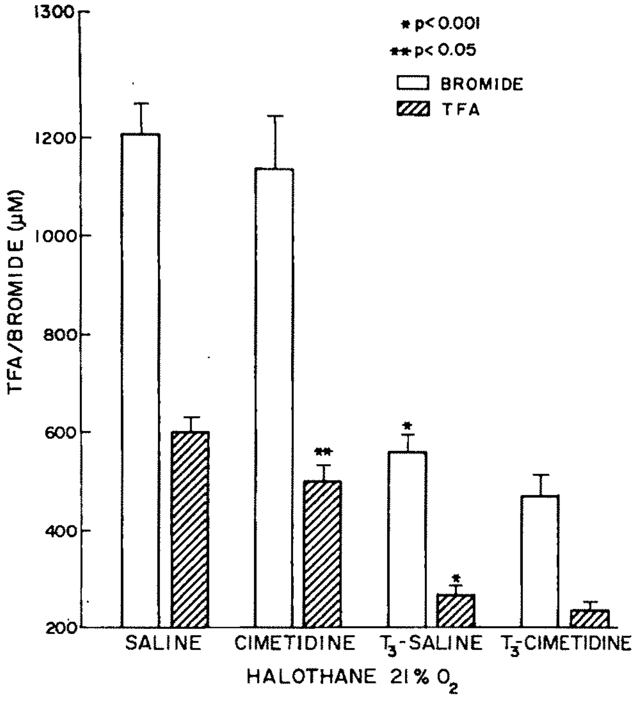

Figure 1. The effect of cimetidine on the oxidative metabolism of halothane in the T_3 model.

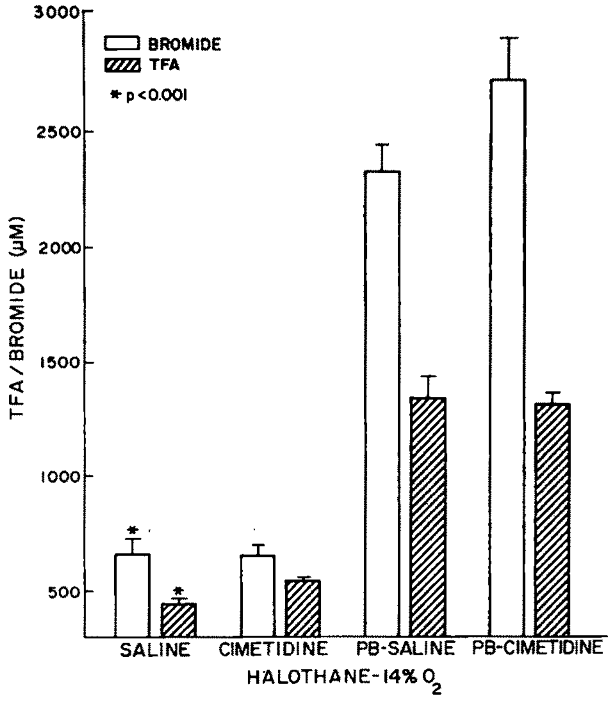

Figure 2. The effect of cimetidine on the oxidative metabolism of halothane in the phenobarbital–hypoxia model.

oxygenase system (18). However, cimetidine appeared to be less effective than N-acetyl cysteine. Both this study and the previous one by Plummer et al. (16) now demonstrate that cimetidine also partially protects against halothane hepatotoxicity in the phenobarbital–hypoxia rat model, possibly because of inhibition of reductive metabolism of halothane. However, cimetidine did not provide protection against hepatic necrosis in the T_3 rat model. This finding is consistent with our previous observations that production of toxic metabolites by either the reductive or oxidative pathways does not seem important in the mechanism of halothane hepatotoxicity in the T_3 model (7). The effects of cimetidine on oxidative halothane metabolism in the T_3 model indicate that oxidative metabolism is markedly reduced in the T_3 model and that cimetidine has no further effect. Smith has also shown that TFA urinary production is decreased in hyperthyroid rats after halothane anesthesia, which is in keeping with our results (19). We have previously demonstrated that T_3-pretreatment decreases cytochrome P-450 in male rats and that a further decrease occurs with halothane anesthesia (6). Thus it is in keeping with these findings that TFA and bromide production is reduced in the T_3 model. In the phenobarbital–hypoxia model both oxidative and reductive metabolism are increased, as assessed by an increase in TFA, bromide, and plasma and urinary fluoride concentrations.

In summary, we have demonstrated that cimetidine produced a significant decrease in methoxyflurane defluorination, but this finding probably has little clinical significance. In contrast, it was more difficult to demonstrate that cimetidine decreases halothane defluorination; however, there is other evidence that cimetidine reduces fluoride production from halothane under conditions of enzyme induction and hypoxia (16), which agrees with our finding that cimetidine reduced halothane hepatotoxicity in the phenobarbital–hypoxia rat model. The clinical importance of this observation is uncertain, because cimetidine did not decrease halothane hepatotoxicity in the T_3 animal model, and it is unknown whether either model is predictive of halothane hepatotoxicity in humans. In addition, cimetidine inhibited the oxidative metabolism of halothane in both 21% and 100% oxygen. Our studies also confirm that hypoxia reduces the oxidative biotransformation of halothane. One unexpected and intriguing observation was that bromide liberation, which is produced by the oxidative pathway, and only to a minor extent by the reductive pathway, appears to be inhibited by hyperoxia as well as hypoxia.

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Naloxone Attenuates Hypoxic Depression of Ganglionic Transmission

Hideki Kuribayashi, MD, PhD, Hiroshi Endoh, MD, Kazunori Sato, MD, Yukio Sato,
Hideho Higashi, MD, PhD, and Koki Shimoji, MD, PhD

KURIBAYASHI H, ENDOH H, SATO K, SATO Y, HIGASHI H, SHIMOJI K. Naloxone attenuates hypoxic depression of ganglionic transmission. Anesth Analg 1986;65:489–92.

The effect of the opioid antagonist naloxone on hypoxia-induced blockade of synaptic transmission in the superior cervical ganglion (SCG) of the rat was studied in vitro. Naloxone (6 × 10^{-6}M or more) attenuated the hypoxia-induced blockade of synaptic transmission in the SCG. In addition, in the concentrations studied, naloxone itself had a blocking effect on ganglionic transmission that involved terminal sites of the preganglionic axons. These data suggest that the protective effect of higher doses of naloxone on the hemodynamic responses to hypoxemia or ischemia may originate at least in part from the attenuating effect of naloxone on the hypoxia-induced blockade of ganglionic transmission.

Key Words: HYPOXIA, GANGLIONIC TRANSMISSION—naloxone. ANTAGONISTS, NARCOTIC—naloxone.

The opioid antagonist naloxone has been reported to have a protective effect in several types of shock and ischemia or hypoxemia (1–3), suggesting that endogenous opioid systems are involved in the pathogenesis of responses to these insults (3). Opioid receptor sites in the central nervous system (CNS) have also recently been demonstrated to be involved in mediation of the effects of endorphins in the presence of ischemia or hypoxemia (4). The effects of naloxone on the CNS could also be mediated at least in part through the autonomic nervous system (ANS). Moreover, enkephalin-positive fibers have recently been observed by immunohistochemical study to be present in mammalian sympathetic ganglia (5). This might imply involvement of enkephalin in synaptic transmission in these ganglia. Electrophysiologic in vitro investigations have disclosed that enkephalin produces postsynaptic hyperpolization and presynaptic inhibition of transmitter release in various autonomic ganglia, and that these actions of enkephalin are antagonized by naloxone (6–9). However, little is known about the effect of naloxone on the ANS in the presence of ischemia or hypoxemia.

In this study we explored the in vitro effect of naloxone on the hypoxic depression of ganglionic transmission using the superior cervical ganglion (SCG) of the rat (10).

Methods

The SCG was removed from decapitated Wistar rats, decapsulated, and immersed in Krebs solution maintained at 30–32°C within an airtight incubation chamber (0.3 × 0.3 × 0.6 ml^3) and superfused at a rate of 2 ml/min (10). The composition of the Krebs solution was the following: NaCl, 117.0 mM; KCl, 4.7 mM; $CaCl_2$, 2.5 mM; $MgCl_2$, 1.2 mM; $NaHCO_3$, 25.0 mM; NaH_2PO_4, 1.2 mM; and glucose, 11.0 mM. The solution was aerated with 95%O_2–5%CO_2 when studies were made in the nonhypoxic state. Supramaximal stimuli were delivered to the preganglionic (cervical sympathetic) nerve via a pair of electrodes imbedded in glycerol (Fig. 1).

Compound action potentials (CAPs) were recorded by a pair of glycerol-insulated electrodes attached to the internal carotid (postganglionic) portion of the ganglion. The signal was differentially amplified (0.5 Hz to 30 KHz), displayed on a storage oscilloscope (Nihon-Kohden VC-10), and recorded on a recticorder.

When the ganglion was made hypoxic, the superfusate was switched to the Krebs solution and equil-

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Address correspondence to Dr. Shimoji, Professor and Chairman, Department of Anesthesiology, Niigata University School of Medicine, Asahi-machi 1, Niigata 951, Japan.

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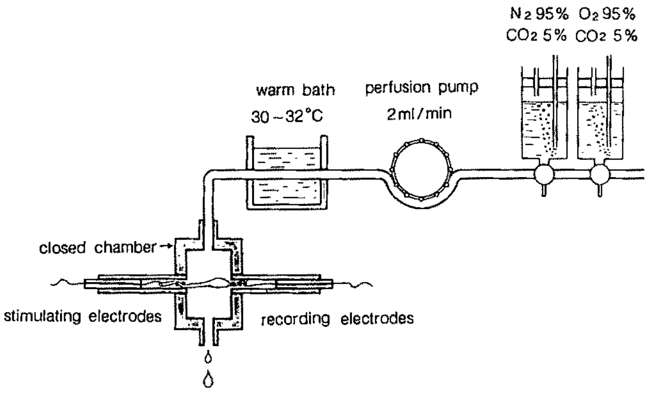

Figure 1. Schematic presentation of experimental arrangements. Locations of stimulating and recording electrodes could be moved by pulling the threads attached to the pre- or postsynaptic nerve trunks.

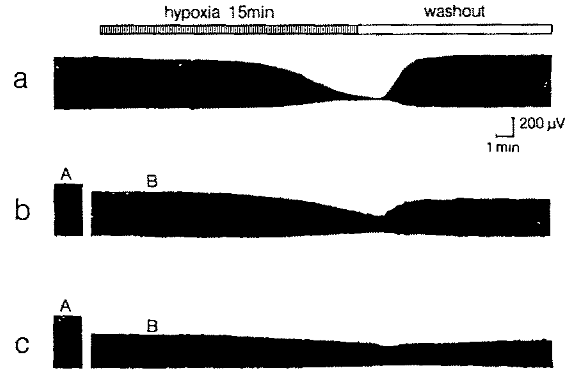

Figure 2. The effect of naloxone on hypoxic depression of the synaptic transmission in rat superior cervical ganglion. The records depicted are the continuous recticorder records of the CAP of the postganglionic trunk (the internal carotid nerve) in response to the supramaximal stimulation of the preganglionic (cervical sympathetic) trunk at 1 Hz. **a**, without naloxone; **b**, treated with naloxone, 6×10^{-6} M; **c**, treated with naloxone, 3×10^{-5} M. **A**, before naloxone; **B**, after naloxone (starting 10 min after exposure to naloxone).

ibrated with 95%N_2–5%CO_2, for 15 min. The ganglion was then allowed to recover in normal Krebs solution saturated with 95%O_2–5%CO_2. The effect of naloxone in concentrations of 6×10^{-7}, 3×10^{-6}, 6×10^{-6}, and 3×10^{-5} M was tested in both oxygenated and hypoxic solutions.

The results are expressed as mean values ± SEM. Statistical significance of observed responses was calculated from the differences between nonpaired observations using Student's *t*-test; a *P* value less than 0.05 was accepted as statistically significant.

Results

In preliminary experiments, we tested the time-course and degree of the hypoxic depression of synaptic transmission in the SCG after switching from the oxygenated solution (Pa_{O_2}, 550 ± 3 torr; mean ± SEM) to the hypoxic solution (Pa_{O_2}, 21.5 ± 1.2 torr). The postganglionic CAP almost disappeared after a 15-min exposure to hypoxia and completely recovered after reoxygenation (Fig. 2).

Naloxone at 6×10^{-6} M or higher suppressed the postganglionic CAP and at the same time reduced the decrease in the postganglionic CAP during hypoxia (Fig. 2, Table 1). The recovery of CAP, however, was prolonged by naloxone (17 ± 3 min with 6×10^{-6} M and 27 ± 4 min with 3×10^{-5} M, compared with 9 ± 4 min without naloxone) ($P < 0.05$ and $P < 0.01$, respectively). Lower concentrations of naloxone (6×10^{-7} M and 3×10^{-6} M) had no significant effect on either ganglionic transmission or its hypoxic depression (Table 1).

When the recording electrodes were located near the ganglion, the postganglionic CAP was usually preceded by a small monophasic potential in amplitude of approximately 10 μv. This potential was evoked by pre- but not by postganglionic fiber stimulation. Application of *d*-tubocurarine (dTC), 1×10^{-4} M, which could completely block nicotinic transmission in the SCG (11), eliminated the postganglionic CAP evoked by the orthodromic stimulation, but did not significantly affect either this small monophasic potential elicited orthodromically or the CAP produced antidromically by the postganglionic fiber stimulation. Thus this small monophasic potential is thought to reflect the action potentials of the presynaptic nerve terminal (10), as previously described in the frog sympathetic ganglia (12). Naloxone, 6×10^{-5} M, reversibly blocked this presynaptic action potential (Fig. 3*B*), whereas the 15-min hypoxic insult suppressed it significantly less (Fig. 3*D*). Amplitude of the presynaptic potential after 6×10^{-5} M naloxone averaged 12 ± 7% ($P < 0.001$; $n = 5$) of the control value; after 15 min of hypoxia the presynaptic action potential averaged 88 ± 5% ($P < 0.05$; $n = 5$) of the prehypoxic value.

Discussion

The present study demonstrates that doses of naloxone that block ganglionic transmission attenuate the depressive effect of hypoxia on SCG transmission. It has been reported that naloxone at relatively low concentrations (≤1–1.5 × 10^{-6} M) antagonizes the depressant effect of enkephalin on synaptic trans-

Table 1. Effects of Naloxone on the Postganglionic Compound Action Potentials (PGCAP) of the Rat Superior Cervical Ganglion under Normoxic and Hypoxic Conditions

	Naloxone concentration (M)			
	6×10^{-7}	3×10^{-6}	6×10^{-6}	3×10^{-5}
PGCAP (% control)				
Normoxia	101 ± 18 (5)[a]	96 ± 7 (7)	88 ± 3[b] (7)	66 ± 5[c] (5)
Hypoxia	4 ± 5 (5)	9 ± 7 (6)	31 ± 7[d] (6)	56 ± 4[d] (5)

Mean ± SEM.

[a] Number of preparations is presented in parentheses.

[b] $P < 0.05$

[c] $P < 0.001$

[d] $P < 0.01$

mission in peripheral autonomic ganglia (6–9). In addition, the present study demonstrates that higher doses ($\geq 6 \times 10^{-6}$ M) of naloxone itself inhibit ganglionic transmission. This dual action of naloxone might account for a partial agonistic effect of naloxone on opioid receptors in the rat SCG. However, this seems unlikely for the following reasons: First, lower concentration of naloxone had no inhibitory effect on the postganglionic CAPs. Second, the present results demonstrate that the blocking action of higher doses of naloxone on ganglionic transmission was due to inhibition of the presynaptic action potentials.

The protective effect of naloxone on the hypoxic depression has been previously demonstrated in the CNS, presumably a result of the antagonistic effect of naloxone on the endogenous opioids in the CNS (13, 14). We could demonstrate in the present study that a similar mechanism prevails in the ANS, because lower concentrations of naloxone ($\leq 3 \times 10^{-6}$ M) significantly affected neither ganglionic transmission nor its hypoxic depression. However, it is conceivable that naloxone not only antagonizes the endogenous opioids in the ganglion, but also blocks the preganglionic terminal to protect it from the rapid decrease in the concentration of acetylcholine stores caused by hypoxia. Lipton and Whittingham (15) also suggested that in the in vitro hippocampal preparation, neurotransmitter disruption would be responsible for the failure of evoked potentials during hypoxia. The present results showing that the transsynaptic activity (the postganglionic CAP) was more sensitive to hypoxia than the presynaptic action potential indirectly support the idea that the depressant action of hypoxia on the ganglionic transmission is due to failure of the presynaptic release of neurotransmitter rather than its blocking effect on the action potential of the preganglionic nerve terminal. The block of ganglionic transmission produced by higher concentrations of naloxone could also be the cause of the delayed recovery of the postsynaptic CAP from hypoxia in the presence of the drug.

The inhibitory effect of naloxone on synaptic transmission was also found in the SCG of the cat and rabbit by Kosterlitz et al. (16). They postulated that the action of a high concentration of naloxone such as 27.5×10^{-6} M is nonspecific. Our findings demonstrate that even a more moderate dose of naloxone, 6×10^{-6} M, can inhibit ganglion transmission in the SCG of the rat. On the other hand, Forbes and Dewey (17) reported that naloxone had no effect on ganglion transmission of the rat SCG at concentrations up to 50×10^{-5} M. The inconsistencies in these reports could be due to differences in either the time of exposure to naloxone or the decapsulation techniques.

The present results have also demonstrated that hypoxia preferentially depresses synaptic transmission rather than spikes signal conduction in the presynaptic terminal.

Few data are available on the effect of hypoxia on synaptic transmission in the SCG (18,19). Whether failure of transmission within the CNS due to hypoxia takes place at pre- or postsynaptic levels remains controversial (20–23). The most recent research on the effect of hypoxia on the CNS has been in in vivo models. Secondary changes such as disturbances of microcirculation or accumulation of metabolites must be considered in the in vivo studies and may account in part for the discrepancies concerning the hypoxic effect on CNS synaptic transmission (24).

The concentration of naloxone, 6×10^{-6} M, that had a significant attenuating effect on the hypoxic depression of the postganglionic CAP in the present study exceeds that achieved in clinical practice ($6 \times 10^{-7} - 3 \times 10^{-6}$ M) but is in the range of concentrations ($6 \times 10^{-6} - 3 \times 10^{-5}$ M) attained in the studies in rats by Holaday et al. on the effect of naloxone in shock (1–4). Differences in naloxone doses among species and preparations must be considered in this regard. Controversial data regarding the effectiveness of naloxone in shock in animals and in clinical studies (25) may result from species differences as well as differences in doses of naloxone used.

Although a more detailed study of underlying mechanisms of the attenuating effect of naloxone on the hypoxic depression of ganglionic transmission is necessary, the effect of naloxone on the sympathetic ganglion as demonstrated in the present study might contribute at least in part to the protective or therapeutic effect of naloxone on hemodynamic responses to ischemia or hypoxemia.

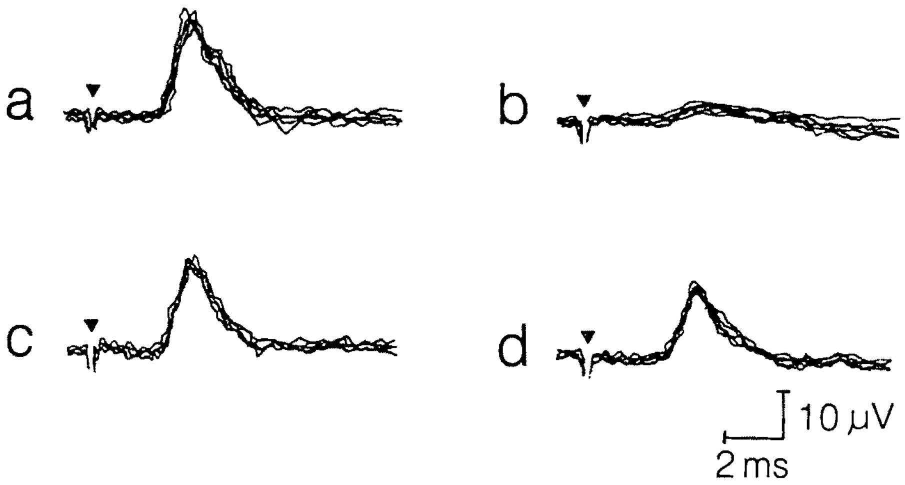

Figure 3. Effect of naloxone on the action potential of presynaptic nerve terminal. The responses recorded from the surface of the ganglion by stimulating the preganglionic nerve trunk consist of three components: the action potential of the presynaptic nerve terminal, the synaptic response, and the compound action potential of the postsynaptic cells. In **a**, the SCG preparation had been pretreated by 15-min superfusion of dTC at the concentration (1×10^{-4} M), which completely blocked the latter two components of postsynaptic cells without affecting the presynaptic action potential. Thus the presynaptic action potential component, preserved well in dTC-containing medium, is shown as a monophasic response in this figure. In **b**, application of naloxone (6×10^{-5} M) to the dTC-containing solution for 10 min blocked the presynaptic potential almost completely. In **c**, 10 min after washout of the drug, the presynaptic action potential has reappeared. In **d**, a subsequent 15 min of the hypoxic insult did not markedly change the response. Each trace represents five superimposed potentials. The inverted triangle in each tracing denotes the point of stimulus.

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Tubocurarine Sensitivity of the Diaphragm after Limb Immobilization

Barbara E. Waud, MD, and Douglas R. Waud, MD, D Phil

WAUD BE, WAUD DR. Tubocurarine sensitivity of the diaphragm after limb immobilization. Anesth Analg 1986;65:493–5.

The effect of immobilization of a limb on subsequent sensitivity of the diaphragm to d-tubocurarine was examined in the guinea pig. A forelimb was immobilized in a plaster cast for 1 or 3 weeks. An isolated nerve-diaphragm preparation was then set up and the sensitivity to d-tubocurarine measured. Parallel assays on a nerve-lumbrical muscle preparation from the limb in the cast were also examined for comparison. The diaphragm from unimmobilized animals showed the normal decreased sensitivity relative to the lumbrical. After immobilization the sensitivity of the lumbrical decreased, whereas that of the diaphragm did not change. Thus in contrast to previously observed behavior in limb muscles, changes in d-tubocurarine sensitivity produced by immobilization do not involve the diaphragm.

Key Words: NEUROMUSCULAR RELAXANTS—*d*-tubocurarine

Patients with conditions predisposing to disuse atrophy show resistance to the effects of the competitive neuromuscular blocking agents (1,2). The phenomenon has been reproduced in dogs with limbs immobilized in a plaster cast (3). When a nerve-muscle preparation was prepared in vitro from a limb that had been immobilized, the ED_{50} for *d*-tubocurarine was elevated (4). Therefore, the immobilization had produced a change in the neuromuscular junction per se. Furthermore, the concentration of *d*-tubocurarine needed to produce neuromuscular block was greater not only in muscles from the immobilized forelimbs, but also in muscles from the contralateral forelimbs and from the hind limbs. The discovery that immobilization of a single limb led to decreased *d*-tubocurarine sensitivity in other limbs as well made us investigate whether the diaphragm was also affected by immobilization; the correct interpretation of responses to peripheral nerve stimulation obviously requires knowledge of expected sensitivity of respiratory muscles.

Methods

The experiments were performed on isolated nerve-muscle preparations obtained from guinea pigs after a period of forelimb immobilization in a plaster cast. The forelimb (side chosen at random) was fixed in a plaster cast from above the elbow to the tips of the digits. To immobilize the lumbrical muscles, care was taken to ensure that the distal opening of the cast did not permit appreciable movement of the digits. When the immobilization was to last 3 weeks, the cast was not only lined with a thin layer of padding to minimize the likelihood that growth could lead to too tight a fit, but it also was changed at about 2 weeks. A collar of cardboard about 10 cm in diameter was mounted around the animal's neck. This collar prevented access to the cast but still allowed the animal freely to move about the cage, to eat, and to drink. (Previously (4) we had demonstrated that the collar alone did not lead to a change in sensitivity to *d*-tubocurarine).

To offset the effect of growth on the size of the guinea pig and muscle at the time of assay, the longer periods of immobilization were started in younger animals. This was successful inasmuch as an analysis of variance at the end of the study showed no significant variation among weight of animals at the time of assay ($F = 1.47$; 2, 15 df).

At the end of the period of immobilization, the diaphragm and its associated nerve were removed along with a nerve-muscle from the limb in the cast. The preparations were mounted in an isolated organ bath for isometric tension recording at the resting tension yielding maximal developed tension. The nerve was mounted in a tunnel electrode and stimulated

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Address correspondence to Dr. B. E. Waud, Department of Anesthesiology, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01605.

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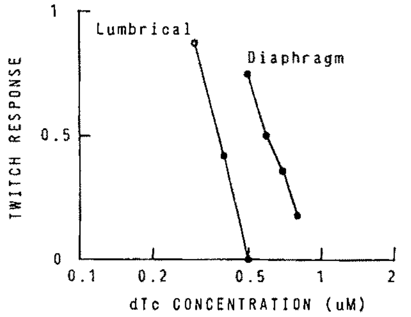

Figure 1. Illustrative experiment. Fractional twitch response to nerve stimulation plotted against concentration of *d*-tubocurarine (μM). Left hand curve, lumbrical muscles; right hand curve, diaphragm.

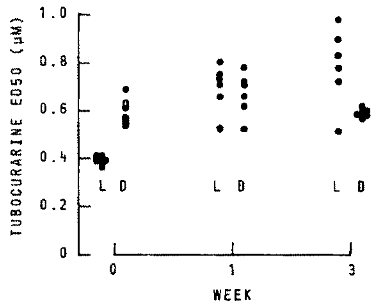

Figure 2. Summary of results. Ordinates: ED_{50} values (μM) for *d*-tubocurarine block of the indirectly elicited twitch response. Abscissae: durations of immobilization in weeks. At each time period the values for the lumbrical muscle are on the left, those for the diaphragm on the right.

every 10 sec with a shock lasting 0.1 msec and at twice the intensity producing a maximal twitch response. The bathing solution was of the following composition (mM): Na^+ 138, K^+ 5.9, Cl^- 118, Ca^{2+} 1.26, Mg^{2+} 1.2, $H_2PO_4^-$ 1.2, SO_4^{2-} 1.2, HCO_3^- 25, lactate 2.5, plus glucose 2.08 g/L, bubbled with 95% O_2/5% CO_2 and kept at 37°C. The drug dilutions were made in a separate chamber at 37°C, and then the final solution was added by overflow (4). The dose–response curve to *d*-tubocurarine was determined by adding the drug in step-wise concentrations selected to span levels of block between none and full. The preparation was equilibrated in the bath for 20–30 min before the assay began, and the drug was left in contact with the preparation until the twitch stabilized at each dose level (about 30 min).

Each dose–response curve was fitted by least squares to the function:

$$Y = 1 - T^S/(T^S + K^S)$$

where Y is the fractional twitch response (1 normally, 0 at complete block), T is the concentration of *d*-tubocurarine, K the ED_{50} (when $T = K$, $Y = 0.5$), and S is a parameter governing steepness of the relationship. The resulting estimates of the ED_{50} were then used in subsequent analyses of variance.

Effects demonstrable at the 95% probability level were considered statistically significant.

Results

Figure 1 presents a sample experiment from a control animal and shows, as expected, that the sensitivity of the diaphragm to *d*-tubocurarine is less than the sensitivity of the lumbrical muscle. Figure 2 summarizes the results from control animals and those in which a forelimb had been immobilized for 1 or 3 weeks. The *d*-tubocurarine ED_{50} values for the lumbrical muscles at 0, 1, and 3 weeks were 0.391 ± 0.006 μM, 0.693 ± 0.039 μM, and 0.786 ± 0.066 μM, respectively. Thus both control ED_{50} values and increases in ED_{50} produced by immobilization are comparable to those found previously (4). The ED_{50} values for the diaphragm at 0, 1, and 3 weeks were 0.600 ± 0.023 μM, 0.667 ± 0.036 μM, and 0.591 ± 0.007 μM, respectively. The control ED_{50} for the diaphragms is greater than the control ED_{50} for the lumbrical muscles, but no increase in the ED_{50} for the diaphragm is seen after limb immobilization.

Statistical analysis confirms the above interpretation. A one-way analysis of variance among the three weekly groups of lumbrical ED_{50} values gives a large and significant F ratio (21.9; 2, 15 df, $P < 0.01$). With the week zero group removed, the F value decreased to 1.5 (1, 10 df), an insignificant value indicating the change occurs in the first week and does not progress subsequently. With the values for the diaphragm, the F value for the three groups was insignificant (2.74; 2, 15 df).

Figure 3 shows the effect of immobilization on the relative sensitivities of diaphragm and lumbrical muscle to *d*-tubocurarine. The ratio of diaphragm: lumbrical muscle at 0 weeks was 1.54 ± 0.07, at 1 week was 0.97 ± 0.06, and at 3 weeks was 0.79 ± 0.08. After immobilization, the two muscles no longer differed in sensitivity.

Discussion

Because the lumbrical muscles in this study behaved similarly to those examined earlier (4), the experimental conditions seem to be comparable, and therefore the two studies can be treated as a unit. That the diaphragm requires a higher concentration of *d*-tubocurarine to produce neuromuscular block than do peripheral muscles has been shown previously in isolated muscles (5) in cats and dogs (6) and in patients (7). Our results agree with these previous studies.

The absence of the change in the ED_{50} of the dia-

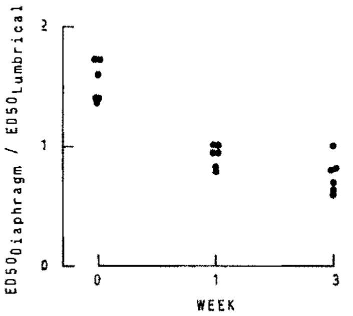

Figure 3. Sensitivity of diaphragm relative to that of lumbrical muscle. Ordinates: ratio of ED_{50} values for the two muscles. Abscissae: durations of immobilization in weeks.

phragm to *d*-tubocurarine after limb immobilization suggests that the decreased sensitivity to *d*-tubocurarine seen in unimmobilized as well as immobilized limbs is a reflection of the level of muscle activity rather than of a circulating humoral agent. The experimental design was such as only to demonstrate the phenomenon, and cannot determine the mechanism of the change.

The guinea pig is not a particularly active animal. However, in this respect it is probably not a poor model for hospital patients who also quite often are not very mobile. Thus it is reasonable to expect that the behavior we find extends to patients.

That immobilization of a limb did not change the ED_{50} value of the diaphragm is important clinically, especially during the reversal of nondepolarizing muscle relaxants. Normally, anesthesiologists measure the response of peripheral muscles to nerve stimulation and assume that, because of the greater margin of safety of the diaphragm when compared to peripheral muscles (6), patients will be able to breathe adequately when the response to peripheral stimulation has returned to control values. In patients who have been bed-ridden or otherwise rendered inactive, however, this assumption may not be true. Indeed, values for diaphragm/lumbrical ratio of less than one in figure 3 indicate that the diaphragm can still be blocked when the peripheral response is normal.

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Intravenous Fluid Temperature, Shivering, and the Parturient

M. Nicholas Workhoven, MD

WORKHOVEN MN. Intravenous fluid temperature, shivering, and the parturient. Anesth Analg 1986;65: 496–8.

The effect of warmed vs room-temperature intravenous fluids is examined for decreasing shivering in parturients undergoing epidural anesthesia for elective cesarean sections. Forty-four women were studied, 22 receiving warmed and 22 receiving room-temperature fluid therapy for preblock prophylaxis of hypotension and intraoperative maintenance and replacement. Of those given room-temperature balanced salt solutions, 64% shivered, as opposed to 14% in the warm fluid group, an observation significant at less than a P of 0.005 by χ^2-analysis.

Key Words: COMPLICATIONS—shivering. TEMPERATURE—intravenous fluids.

Parturients arriving in operating rooms for elective cesarean sections increasingly look to the anesthesia team to provide safe analgesia and a comfortable environment for a family-oriented birth (1). Shivering, often intense and uncontrollable, is very disruptive to the parturient and her spouse or friend (2). Shivering brings adverse physiologic changes as well. Prior to regional anesthesia, it is customary to give 1 L or more of crystalloid to minimize postblock hypotension (1,3,4,5). This simple study was devised to see if the temperature of the intravenous (IV) fluids altered the incidence of intraoperative shivering.

Methods

Forty-four ASA class I or II term pregnant women presenting for elective cesarean section were studied. On an alternating basis, 22 patients were put into the room-temperature IV fluid group (group 1) and 22 into the warm IV fluid group (group 2). Fluids were heated in a warming cabinet and taken out to be administered immediately. A mercury thermometer gave ambient operating room temperatures and therefore group 1 fluid temperatures of 20.0–22.2°C; cabinet temperatures and group 2 crystalloid temperatures were 30.0–33.9°C. Each patient received 1 L of lactated Ringer's or Normosol-R solution given over 10–15 min through an unrestricted large bore IV catheter. A second liter of the same fluid with 2.5 or 5% dextrose was given at a rate dictated by maternal blood pressure. Never was more than 500 ml of the second liter required prior to delivery. Blood pressure was further supported by a wedge under the right hip, modest leg up tilt to the operating room table, and, infrequently, small doses of ephedrine as IV bolus or continuous infusion (Table 1). Blood pressure thus was kept within 20% of preoperative baseline and not less than 100 mm Hg systolic. No attempt was made to warm the operating room, but the patient was covered throughout as completely as possible by warm blankets.

In all cases, anesthesia was single injection lumbar epidural using room temperature lidocaine, 2%, with epinephrine, 1:200,000 from single-dose vials. A 3-ml test dose was followed by an induction dose of 17–22 ml of the drug. Sensory levels were measured at T4–7 by alcohol swab to loss of temperature sensation.

Small doses of fentanyl, thiopental, or both were given IV pre- and postdelivery for mild sedation as necessary (Table 1).

Patients were observed for shivering in the operating room. Spastic, sustained hypertonic muscle contractions often noted after general inhalation anesthesia were not seen in these patients. Patients were considered to shiver when they had more than 5 min of rhythmic mild, moderate, or severe intermittent muscle contractions with the brief and discontinuous periods of relaxation seen typically in hypothermia.

Parturients with fever, hemoglobin levels less than 10 g/dl, or shivering on arrival in the operating room were excluded. Temperatures were measured orally preoperatively and on arrival in the recovery room. Mean parturient age, height, weight, and hemoglobin levels were similar (Table 2).

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Address correspondence to Dr. Workhoven, Anesthesia Department, Bay Area Hospital, 1775 Thompson Road, Coos Bay, OR 97420.

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Table 1. Supplemental Drugs: Frequency and Mean Dose

Drug	Group 1 Incidence	Group 1 Mean dose	Group 2 Incidence	Group 2 Mean dose
Ephedrine (mg)	5/22 (23%)	13	4/22 (18%)	25
Fentanyl (μg)	15/22 (68%)	128	16/22 (73%)	85
Thiopental (mg)	10/22 (45%)	130	9/22 (41%)	122

Table 2. Patient Demographics[a]

	Age	Height (cm)	Weight (kg)	Hemoglobin (gm/dl)
Group 1	25.4	163.7	78.8	12.2
Group 2	27.8	162.5	73.3	12.7

[a] Means.

Table 3. Incidence of Shivering

	Shivering	Not shivering	Total
Group 1	14	8[a]	22
Group 2	3	19[a]	22

[a] Significant statistically ($P < 0.005$ by χ^2 analysis).

Protocol approval was granted by the Executive Committee of the medical staff, acting in the absence of any human use review committee in our institution.

Data were analyzed for statistical significience by the χ^2-test. The Yates correction for continuity was applied.

Results

In group 1, 14/22 (64%) had gross, often intense shivering during the intraoperative period, generally lasting much longer than 5 min. In contrast, only 3/22 (14%) of the parturients in group 2 showed such shivering (Table 3), and it tended to be less intense and of short duration. This was a statistically significant difference ($P < 0.005$).

Analysis of patient temperature information (Table 4) revealed that patients in group 1 who shivered stayed warmer than those who did not. In group 2, temperatures decreased about equally irrespective of the presence of shivering.

Discussion

Shivering in patients undergoing peridural anesthesia has been noted 20–50% of the time (6,7). Its effects are adverse physiologically and perhaps psychologically. Shivering can increase oxygen consumption (8) up to 500% (9), increase cardiac work (7,9), and decrease P_{O_2} (9,10,11). Increased demand on ventilation also occurs (7). Patients with decreased cardiac or pulmonary reserves may be threatened (7). Anaerobic metabolism can develop, along with varying degrees of metabolic acidosis (7,12), respiratory acidosis (12), and resultant further deterioration of cardiopulmonary function (7).

No such physiologic complications of shivering were noted in these patients, although one parturient receiving warmed fluid did become diaphoretic and complained of feeling warm. She was dropped from the study. No attempt was made to examine psychologic effects here.

Shivering can also detract from the birth for parturient (6) and spouse, disrupting the family-oriented birth sharing that has moved from the delivery to operating rooms (1). Ostheimer and Datta (2) have noted that of all the side effects associated with anesthesia and birth such as nausea, vomiting, headache, and bladder catheterization, shivering alone was the only symptom particularly mentioned as a disconcerting and unacceptable part of the birth experience.

Many theories have been advanced to explain why these patients shiver. Such muscle activity serves to increase body heat production (6,10). Surprisingly, there seems no solid association between body heat loss and shivering (7,13,14). Holdcroft et al. (14) did find greater heat loss with major regional anesthesia than with general anesthesia, probably associated with a greater degree of peripheral vasodilation and increased skin blood flow related to the sympathetic blockade. Also, in the recovery room, patients who have had conduction anesthesia rewarm more slowly than those having had general anesthesia, even when they shiver in their upper extremities. Webb et al. (6) found that the temperature of the local anesthetic injected to achieve peridural anesthesia did not affect the incidence of shivering. They saw a 31.2% incidence of shivering during epidural anesthesia where no effort was made to infuse IV fluids rapidly.

Interpretation of temperature changes in this study indicate that, in group 1 patients, those who shivered better retained their core temperatures than those who did not shiver, though the nonshiverers had lost more than a half degree centigrade. Temperatures in group 2 patients all decreased about the same amount as in

Table 4. Oral Temperatures (Mean °C)

	Number	Preoperative	Recovery room	Decrease
Group 1				
Total group	22	36.6	36.3	0.3
Shivering group	14	36.6	36.5	0.1
Nonshivering group	8	36.5	35.9	0.6
Group 2				
Total group	22	36.6	36.1	0.5
Shivering group	3	36.6	36.1	0.5
Nonshivering group	19	36.7	36.1	0.6

group 1, whether they shivered or not. Those who did shiver did so less intensely and for briefer periods overall than those who shivered in group 1, thus creating less of a thermogenic effect.

It is recognized that the alternating method used in this study for separating patients into the two groups does not represent true randomization. Despite this flaw, the data presented are so strongly suggestive that further study appears in order.

It seems clear that there is a high basic incidence of shivering with major conduction anesthesia. Rapid infusion of IV fluids may dramatically alter the rate of shivering, depending on the temperature of the fluids. Thus room-temperature fluids may increase the incidence of shivering, and warmed fluids rapidly infused into parturients about to undergo elective cesarean section may very well, by lowering the incidence of shivering, make the experience safer and more satisfying.

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Epidural Morphine for Postoperative Pain Relief in Anorectal Surgery

Ayşe Gürel, MD, Nalan Ünal, MD, Murat Elevli, MD, and Ali Eren, MD

GÜREL A, ÜNAL N, ELEVLI M, EREN A. Epidural morphine for postoperative pain relief in anorectal surgery. Anesth Analg 1986;65:499–502.

Postoperative analgesia and side effects of a single dose of 20 ml of 2% epidural prilocaine followed immediately by either morphine (3 mg in 3 ml saline) or saline (3 ml) were studied in 79 patients scheduled for anorectal surgery. Pain relief was evaluated by a linear scale for 24 hr and by an assessment of the requirement for parenteral analgesics. Of the patients given epidural morphine, 25% did not require analgesics, whereas all patients given prilocaine alone asked for additional analgesia. Remaining patients given morphine were pain-free for a mean duration of 7.6 ± 5.1 hr (SD). Only 9% of patients given morphine required a maximum of three analgesic parenteral injections in 24 hr. Urinary retention was the most prominent side effect observed in patients given epidural morphine. No early or delayed respiratory depression was noted in our patients.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—morphine. ANALGESICS—morphine. PAIN—postoperative.

Epidural morphine is being used increasingly (1–4) and, in some institutions, routinely (5), for relief of postoperative pain. It is generally administered at completion of surgery through a catheter placed epidurally before or after the operation.

The duration of operative anesthesia for anorectal surgery is brief, and a single dose of epidural prilocaine will generally suffice. We therefore conducted a study in which a single dose of prilocaine followed immediately by a single dose of morphine was injected into the lumbar epidural space to evaluate the possible effects of dilution of the narcotic analgesic by the local anesthetic on the intensity and duration of postoperative pain.

Methods

Seventy-nine patients undergoing anorectal surgery were studied. They were divided into two groups (A and B) according to the wards, A or B, in which they were hospitalized. A detailed explanation of the nature and purpose of the study was given to the patients during the preoperative visit.

Thirty minutes before anesthesia, all patients were given flunitrazepam (2 mg) and atropine (0.6 mg) intramuscularly for premedication. With the patient in the lateral position, a Tuohy needle was introduced at the L3-4 interspace. After identification of the epidural space by the "hanging drop" technique, 5 ml of prilocaine 2% solution were injected as a test dose. When no signs of intrathecal or intravascular injection were noted after 4 min, the remaining 15 ml prilocaine were injected, followed immediately by either 3 mg morphine in 3 ml saline, 0.9%, (Group A, $n = 44$) or 3 ml plain saline solution (Group B, $n = 35$). The Tuohy needle was then withdrawn and the patient placed in the supine position with a head-tilt of 30°. Surgery started 15 min after injection of the prilocaine.

Pulse rate, blood pressure, and respiratory rate were recorded in the operating room. The patients were especially observed for nausea or pruritus.

At completion of surgery, patients were taken to the intensive care unit where they remained for the next 24 hr. Postoperative follow-up included the recording of blood pressure and pulse rate, the objective and subjective evaluation of pain, the assessment of parenterally administered analgesics, and the incidence of side effects. The time of onset of postoperative pain was noted for each patient.

Objective pain assessment was made in the intensive care unit 4, 8, 12, 16, 20, and 24 hr postoperatively by nurses unaware of the group to which the patient belonged. The nurses graded the intensity of pain on

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Address correspondence to Dr. Gürel, Dicle University, Faculty of Medicine, Anesthesiology and Reanimation, Diyarbakir, Turkey.

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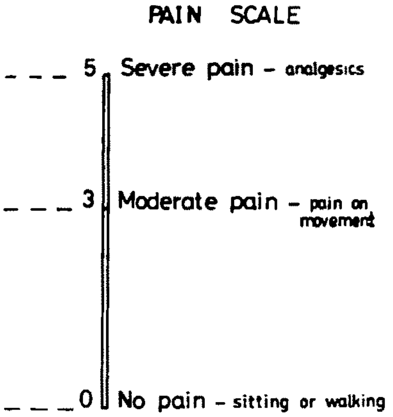
PAIN SCALE
5 Severe pain - analgesics
3 Moderate pain - pain on movement
0 No pain - sitting or walking

Figure 1. Objective pain assessment. The nurses graded the intensity of pain on the linear scale by observing the patient every 4 hr. Score: 5, frequent need for analgesics; 3, pain on movement, reluctant to get out of bed; 0, sits in bed, walks around easily.

a vertical scale, the bottom of the scale, scored 0, representing no pain (the patient could sit up in bed or walk around without difficulty) and the top scored 5, representing severe pain (the patient frequently asked for analgesics) with moderate pain scored 3 (the patient had pain on movement and was reluctant to get out of bed) (Fig. 1). A score of 0 was assigned when patients were found to be asleep. The total number of parenteral analgesics was also recorded during the first 24 hr.

On the morning of the first postoperative day, an anesthetist unaware of the nature of the epidurally injected solutions visited the patients to inquire whether untoward symptoms such as pruritus, nausea, and difficulty with micturition had developed and to evaluate the subjective postoperative pain (no pain, mild pain, acceptable pain, and unbearable pain). Data are expressed as mean ± SD. Results were analyzed using Student's t-test and the χ^2 test.

Results

The mean ages and weights of the two groups were comparable (Table 1). The mean duration of surgery in groups A and B was 39 ± 19.9 min and 34.1 ± 15.4 min, respectively. On viewing the pain scales, it was apparent that the patients in group A experienced significantly less ($P < 0.005$) postoperative pain than the patients in group B (Fig. 2). Morphine analgesia in group A lasted 4–16 hr with a mean of 7.6 ± 5.1 hr, whereas 66% of the patients in group B experienced "severe pain" as soon as the analgesia afforded by the local anesthetic wore off. The duration of epidural block in group B for pain at the operative site was 127 ± 15.1 min.

Table 1. Patient Data and Duration of Operation[a]

	Morphine group (n = 44)	Saline group (n = 35)
Age (yr)	40.5 ± 13.9	38.1 ± 15.0
Weight (kg)	63.7 ± 12.8	52.9 ± 10.7
Duration of operation (min)	39.2 ± 19.9	34.1 ± 15.4

[a] Mean ± SD

During the interview on the first postoperative day, 70% of the patients in group A expressed no pain, whereas none of the patients in group B were pain-free. In fact, 40% of the latter group experienced "unbearable pain" at the time of the interview (Table 2).

Figure 3 shows the number of analgesic injections required by each group of patients. In the morphine group, 25% of the patients were pain-free and required no supplemental analgesics. The number of analgesics required by the rest of the patients in this group was significantly less than that required by patients in the control group ($P < 0.005$).

The most frequent side effect in group A was urinary retention (79%). Of the patients with urinary retention, 49% were eventually able to void spontaneously; the remaining patients required catheterization. Four patients in group A complained of pruritus, one was nauseated, and one vomited.

Approximately 32% of the patients in group B experienced disturbances of micturition. Pruritus and nausea were never observed after epidural saline. The side effects encountered by patients in both groups are summarized in Table 3.

Discussion

Systemic narcotic analgesics are usually the drugs of choice for postoperative pain relief in patients undergoing anorectal surgery (6) with consequent systemic side effects (7). However, the identification of opiate receptors in the substantia gelatinosa of the spinal cord (8) has led to new concepts in the management of acute and chronic pain (9,10). For purposes of postoperative pain relief, morphine is being injected epidurally, usually via a catheter placed either preoperatively in patients selected for operative epidural anesthesia (1) or postoperatively in cases operated upon under general anesthesia (2,3). Through this catheter morphine is given intermittently or as a continous infusion (4).

Because of the short duration of anesthesia required for anorectal operations, we made no attempt in the present study to insert an epidural catheter in our patients. Instead the patients were given a single

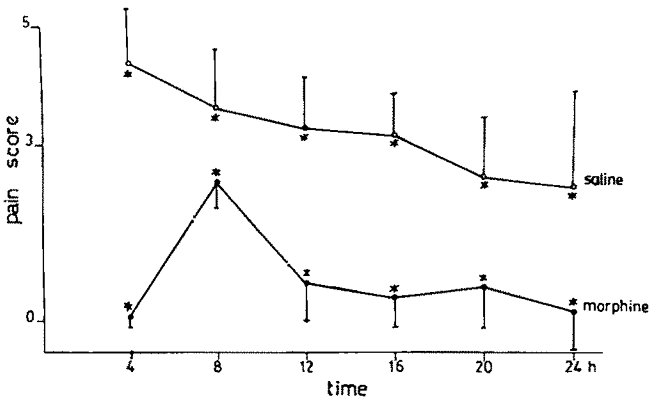

Figure 2. Mean pain scores (± SD) for 24 hr after epidural morphine and epidural saline. Asterisk signifies $P < 0.005$ between scores obtained with morphine and saline (t-test).

Table 2. Subjective Pain Assessment on First Postoperative Morning

	Morphine group (n = 44)	Saline group (n = 35)
No pain (%)	70	—
Mild pain (%)	19	17
Acceptable pain (%)	11	43
Unbearable pain (%)	—	40

dose of 20 ml prilocaine 2% solution epidurally, followed immediately by epidural injection of morphine through the same needle. Thus they experienced a smooth transition from local anesthetic analgesia to morphine-induced pain relief. This technique also had the advantage of compensating for the slow onset of epidural morphine analgesia observed in some patients (11,12).

Local anesthetics block sensory, sympathetic, and motor fibers, whereas morphine binds to specific opiate receptors on the spinal cord to interrupt pain pathways (13). Owing to the difference in the sites of action of these drugs, no interaction was observed in the effectiveness of each when both were used together. The results in the present study revealed that 25% of patients given epidural morphine were completely pain-free and did not require parenteral or oral analgesics postoperatively. Only one hemorrhoidectomy patient experienced pain as early as 4 hr after the operation. The mean duration of pain relief was 7.6 ± 5.1 hr (SD) in patients given epidural morphine, which contrasts with the onset of pain as soon as the local anesthetic analgesia wore off in the control group.

The relation between the dose of epidurally administered morphine and the duration of postoperative pain relief is controversial. Bromage et al. (14) found that an average of 7.6 mg of epidural morphine was necessary for pain relief following lower abdominal surgery. However, in our study we obtained satisfactory analgesia with 3 mg of morphine. Lanz et al. (1) reported similar periods of pain relief with higher doses. Others (5) reported good analgesia with morphine doses less than 5 mg.

When patients in our study given epidural morphine did experience pain, this was quickly resolved by a single dose of dipyrone. The occurrence of intermittent painful episodes during a basal state of analgesia suggests the possible involvement of other nonopiate pain pathways in the spinal cord. The mean pain scores in both our groups of patients decreased gradually over 24 hr, but never exceeded a score of 3 in the morphine group (Fig. 2).

On the first postoperative morning, none of the patients expressed "unbearable pain" in the morphine group, contrasting with 40% in the control patients (Table 2). Of the 40% that had "unbearable pain," 37% were hemorrhoidectomy patients who were most incapacitated by postoperative pain.

Epidural morphine is shown to have decreased the postoperative analgesic requirement (1). Even though patients in the control group were given dipyrone injections on demand, they still suffered from pain during their stay in the hospital. Fifty-seven percent of the patients in this group required four or more analgesic injections, whereas 9% of patients in the morphine group required a total of 3 injections in 24 hr (Fig. 3).

Various side effects caused by epidural morphine have been reported in previous studies (15–17). These side effects are not attributable to the concentration of morphine in the plasma because the quantity of morphine in the blood compartment is dismissed as insignificant even when high doses are used (16). The rostral spread of the narcotic is held responsible for these side effects (18).

In our study one patient experienced nausea and another vomited at the first intake of fluid on the evening of the operative day (Table 3). Macdonald and Bickford-Smith (5) observed a worsening of nausea in obstetric patients upon mobilization about 8–12 hr postoperatively. Our patients were ambulatory starting 6 hr postoperatively, but the incidence of nausea and vomiting was very low. Four patients given epidural morphine had pruritus involving the groin and trunk, but none requested treatment (Table 3).

Delayed respiratory depression is reported in aged, poor risk patients (19), in cases where epidural morphine is supplemented with intravenous nonnarcotic drugs (17), in patients given intermittent injections of epidural morphine (4), and in studies where high doses

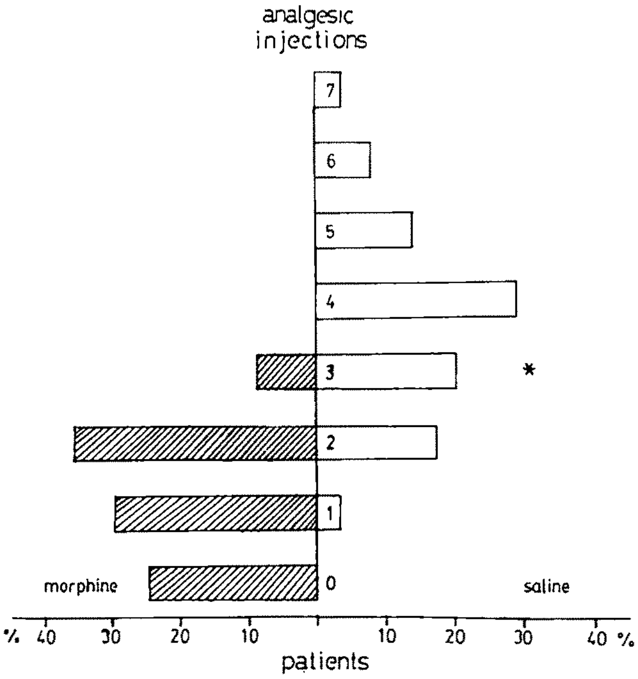

Figure 3. Analgesic requirements in the morphine and saline groups. Asterisk signifies $P < 0.005$ when patients that received three or more analgesic injections in the morphine group are compared with patients who required three or more analgesics in the saline group (χ^2 analysis.)

of morphine are used (18). In this study, the single, low dose of morphine eliminated the danger of early and delayed respiratory depression.

Of the patients in the control group, 32% had difficulty with micturition, but a majority (83%) of these patients were able to void spontaneously in the first 12 hr. In the morphine group urinary retention developed in the first 12 hr. These patients felt discomfort in the second 12 hr due to bladder distention, and 51% eventually had to be catheterized (Table 3). One elderly patient needed catheterization twice.

This study shows that effective and prolonged postoperative analgesia can be achieved when morphine is administered in combination with a local anesthetic into the epidural space in rectal operations associated with severe postoperative pain. In fact our surgical clinics now routinely administer low doses of morphine to patients scheduled for surgery with epidural anesthesia. The frequent need for catheterization appears to be the major drawback of this technique of pain relief.

We thank the nursing staff of the surgical intensive care unit for their valuable help and cooperation. We thank Ms. Meral Aktan for her valuable secretarial help.

Table 3. Side Effects

	Morphine group ($n = 44$)	Saline group ($n = 35$)
Pruritus (%)	9	—
Nausea (%)	2	—
Vomiting (%)	2	—
Urinary retention (%)	79	32
Voided spontaneously (%)	49	83
Respiratory depression (%)	—	—

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Rapid Sequence Induction Using Vecuronium

Vimala E. Kunjappan, MD, Eli M. Brown, MD, and Gaylord D. Alexander, MD

KUNJAPPAN VE, BROWN EM, ALEXANDER GD. Rapid sequence induction using vecuronium. Anesth Analg 1986;65:503–6.

The purpose of this study was to determine the ideal priming and total dose of vecuronium when used as the relaxant during rapid sequence induction of anesthesia and tracheal intubation. Seventy patients were studied. Various priming and total dose schedules using vecuronium were compared with succinylcholine, 1.5 mg/kg. The mean onset times, intubating conditions, and mean duration times were compared. A priming dose of 10 µg/kg produced good intubation conditions with both 70 µg/kg and 150 µg/kg (total doses), but the mean onset times remained significantly longer than succinylcholine 1.5 mg/kg ($P < 0.05$). A priming dose of 15 µg/kg of vecuronium with 100 µg/kg total dose, on the other hand, not only produced excellent intubating conditions but also resulted in a mean onset time not significantly different from succinylcholine, 1.5 mg/kg. This latter dose schedule of vecuronium is recommended for rapid sequence induction when succinylcholine is contraindicated. Vecuronium is preferable to pancuronium for rapid sequence induction because of its lack of cardiovascular side effects and short duration.

Key Words: NEUROMUSCULAR RELAXANTS—vecuronium. INDUCTION, ANESTHESIA—rapid sequence.

Rapid sequence induction is used to secure the airway in emergency surgical procedures in order to avoid aspiration of gastric contents. Succinylcholine is ordinarily the relaxant of choice because of its rapid onset of action. However, succinylcholine may produce muscle fasciculations, myalgia (1,2) and increases in intragastric (3), intraocular (4,5) and intracranial pressures (6). Succinylcholine should also be avoided in patients with burns (7), renal failure (8), and in patients with a history of malignant hyperthermia or pseudocholinesterase deficiency.

Pancuronium in large doses (0.15 mg/kg) is presently the relaxant most often used when succinylcholine is contraindicated (9). However, pancuronium may produce adverse cardiovascular effects, such as hypertension and tachycardia, in some patients. In addition, in short surgical procedures, patients may have to be mechanically ventilated postoperatively because of the prolonged duration of action of pancuronium (9).

The introduction of a nondepolarizing intermediate-acting muscle relaxant, vecuronium, that is essentially free of cardiovascular side effects prompted us to investigate its efficacy for rapid sequence induction of anesthesia and tracheal intubation. The effect of various priming and intubating doses on onset time and clinical duration time were studied.

Methods

Seventy patients were studied. Approval for the study was obtained from the hospital committee for research on human subjects. All patients in the study signed informed consents. The age range was 17–83 yr and weight range 50–127.4 kg. There were 62 women and 8 men. Seven groups of ten patients each were studied. One group, the "standard" group, was given succinylcholine, 1.5 mg/kg, for tracheal intubation. The remaining six groups received vecuronium according to the dose schedule in Table 1. The ECG, blood pressure, and heart rate were monitored in all patients. A constant current peripheral nerve stimulator (Myoscan) was used to monitor the muscle blockade. A total of 300–400 g tension was applied to the thumb. The ulnar nerve at the wrist was stimulated through surface electrodes by supramaximal impulses of 0.2 msec duration at 0.1 Hz. The twitch tension of the adductor pollicis was noted. Train of four (T4), 2 Hz stimuli were applied prior to the intubating dose of vecuronium. An assistant observed and recorded the presence of all four twitches at this time. The onset time was defined as the time from the injection of the intubating dose of muscle relaxant to the time when all four twitches disappeared. The duration time was defined as the time from the injection of intubating dose of muscle relaxant to the

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Address correspondence to Dr. Kunjappan, Department of Anesthesiology, Sinai Hospital of Detroit, 6767 West Outer Drive, Detroit, MI 48235.

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Table 1. Treatment Groups

Groups	n	Drug	Dose		
			First dose	Second dose	Total
Standard drug	10	Succinylcholine	1.5 mg/kg[a]		
Group A	10	Vecuronium	7 μg/kg	63[b]	70
Group B	10	Vecuronium	10	60	70
Group C	10	Vecuronium	10	140	150
Group D	10	Vecuronium	15	135	150
Group E	10	Vecuronium	15	85	100
Group F	10	Vecuronium	150[a]		

[a] One dose only.
[b] All doses given in μg/kg unless otherwise indicated.

Table 2. Onset Times and Duration of Muscle Blockade

Groups (n = 10)	Onset times (sec)	P value	Duration (min)
Standard (Succinylcholine)	58 ± 4.16	—	6.5 ± 0.73
Group A	246 ± 27.5	0.000[a]	15.9 ± 1.73
Group B	216 ± 29.95	0.000[a]	16.1 ± 2.20
Group C	141.5 ± 13.75	0.001[a]	33.3 ± 4.70
Group D	75.50 ± 9.96	0.474	39.7 ± 4.34
Goupr E	81.50 ± 2.69	0.337	28.4 ± 4.31
Group F	138.00 ± 10.21	0.002[a]	37.2 ± 6.81

All values are mean ± SEM.
[a] Significantly different from standard group (succinylcholine), $P < 0.05$.

time when the first twitch reappeared. Onset time (in seconds) and duration of muscle blockade (in minutes) was recorded for each patient.

The patients received fentanyl, 100 μg, prior to the administration of the priming dose of vecuronium. Patients that received vecuronium were informed that their eyelids might feel heavy and that they might have blurred vision. They were instructed to notify the anesthesiologist of any respiratory difficulty that occurred. The patients breathed 100% oxygen by mask after the priming dose, and their respiratory tidal volumes were closely monitored. The initial response to train-of-four stimulation was determined as soon as the patient became unconscious after administration of thiamylal, 4–5 mg/kg, approximately 4 min after administration of the priming dose of vecuronium. Immediately thereafter, the remainder of the total dose of vecuronium was administered. Cricoid pressure was applied. All intubations were attempted at 60 sec; the time when all twitches disappeared after the total dose and the time when the first twitch reappeared were recorded. Anesthesia was maintained with N_2O/O_2, 4L/2L. Additional doses of 50–100 mg of thiamylal and 50–100 μg of fentanyl were administered if further analgesia was considered necessary. Ease of intubation was graded as 3 (excellent), no movement of cords; 2 (good), slight movement of cords; or 1 (poor), coughing and bucking. Vecuronium was reversed at the conclusion of surgery in all patients. Thirty patients received glycopyrrolate, 0.015 mg/kg, and neostigmine, 0.07 mg/kg; forty patients received glycopyrrolate, 0.015 mg/kg, and pyridostigmine, 0.3 mg/kg. Adequacy of reversal was determined both by peripheral nerve stimulator and the ability to sustain head lift.

Data were statistically analyzed by one-way analysis of variance comparing the seven study groups. Pair-wise comparisons were done between the standard group and each of the other groups. $P < 0.05$ was considered statistically significant (Table 2).

Results

Intubating conditions were not satisfactory within 60 sec when a single large dose (150 μg/kg) of vecuronium was used. Only six of ten patients could be intubated in 60 sec. When a priming dose of vecuronium was used 5 min before the total dose, all the patients could be intubated in 60 sec. Only five of the ten patients given 7 μg/kg priming dose had a score of 3 for intubation. However, when 10 μg/kg and 15 μg/kg priming doses were employed, 38 of 40 patients had a score of 3, indicating excellent intubating conditions (Table 3).

The mean onset time closest to that seen with succinylcholine occurred in patients in groups D (15 μg/150

Table 3. Intubation

Dose (prime/total)	Groups	Time of intubation: Time (sec)	Time of intubation: Number of patients	Score of intubation: Score	Score of intubation: Number of patients
Succinylcholine 1.5 mg/kg	Standard Drug	60	10	3	10
				2	0
				1	0
Vecuronium 7μg/70μg	Group A	60	10	3	5
				2	5
				1	0
10μg/70μg	Group B	60	10	3	9
				2	1
				1	0
10μg/150μg	Group C	60	10	3	10
				2	0
				1	0
15μg/150μg	Group D	60	10	3	9
				2	1
				1	0
15μg/100μg	Group E	60	10	3	10
				2	0
				1	0
0/150μg	Group F	60	10	3	6
					4[a]

[a] Insufficient relaxation for intubation at 60 sec; in the four patients, two intubations were successful at 90 sec with a score of 2, and two at 120 sec, also with a score of 2.

μg) and E (15 μg/100 μg), where a priming dose of 15 μg/kg was used ($P > 0.05$). All other groups showed significantly longer onset times ($P < 0.05$) (See Table 2).

The longest duration time (39.7 min) was seen with a total dose of 150 μg/kg vecuronium. The 100 μg/kg total dose was associated with a duration that averaged 28.4 min (Table 2).

Discussion

Rapid onset of muscle relaxation with divided doses of vecuronium and atracurium has been described by Schwartz et al. (10) and Mehta et al. (11). In Schwartz's study, when vecuronium was used for priming, even though intubation was accomplished in 60–80 sec, the intubation score was not consistently good. Seven of 40 patients had a score of 2 for intubation, indicating diaphragmatic movement. Better intubating conditions are necessary for rapid sequence induction, especially in patients who have a penetrating eye injury or increased intracranial pressure. In our study, 10 μg/kg vecuronium as a priming dose provided good intubating conditions when used as part of total doses of 70 μg/kg or 150 μg/kg, but the onset time remained longer than that seen with succinylcholine, 1.5 mg/kg. On the other hand, a priming dose of vecuronium, 15 μg/kg, with 100 μg/kg total dose produced not only a mean onset time that was not significantly different from the mean onset time produced by succinylcholine, 1.5 mg/kg, but also excellent intubating conditions. For rapid sequence induction and intubation to be consistently reliable, a nondepolarizing muscle relaxant must not only produce good intubating conditions but should also have an onset time approximating that associated with a paralyzing dose of succinylcholine. Our study demonstrates that a priming dose of vecuronium, 15 μg/kg, followed 5 min later by the remainder of a total dose of 100 μg/kg, fulfills these requirements. Consequently, a priming dose larger than 15 μg/kg is unnecessary and may produce unacceptable symptoms in awake patients. Indeed, a dose of 15 μg/kg of vecuronium produced heavy eyelids and blurred vision, but these symptoms were tolerable as long as the patient was forewarned. Train-of-four response was not affected by this dose. In addition, 50–100 μg fentanyl administered just prior to the priming dose greatly ameliorated these symptoms. Two of our patients complained of difficulty in swallowing, but no patient had frank respiratory embarrassment. If difficulty in breathing or swallowing occurs, the patient should be anesthetized without waiting the full 4 min, because these symptoms indicate partial muscle blockade.

In conclusion, we recommend that where rapid sequence induction is indicated and succinylcholine is contraindicated, a priming dose of 15 μg/kg of vecuronium, followed 5 min later by a total dose of 100 μg/kg, can be safely used as an alternate technique for rapid sequence induction. The mean clinical duration time of 28.4 min after this dose of vecuronium is not unreasonably long for most surgical procedures.

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The Effects of Nicardipine on Cerebrospinal Fluid Pressure in Humans

Toshiaki Nishikawa, MD, Keiichi Omote, MD, Akiyoshi Namiki, MD, PhD, and
Takeo Takahashi, MD, PhD

NISHIKAWA T, OMOTE K, NAMIKI A, TAKAHASHI T. The effects of nicardipine on cerebrospinal fluid pressure in humans. Anesth Analg 1986;65:507–10.

The effects of nicardipine hydrochloride, a calcium channel blocker, upon cerebrospinal fluid pressure (CSFP) were investigated in 47 patients without intracranial pathology who were assigned to one of three groups: group 1 (n = 17), who received 0.01 mg/kg nicardipine, group 2 (n = 17), who received 0.02 mg/kg, and group 3 (n = 13), who received 0.03 mg/kg. A spinal needle was inserted into the subarachnoid space to permit continuous measurement of CSFP. Nicardipine produced statistically significant increases in CSFP: from a mean of 7.6 to 11.6 mm Hg in group 1, 7.2 to 12.2 mm Hg in group 2, and 7.4 to 13.8 mm Hg in group 3 (P < 0.001 in each group). CSFP after nicardipine attained its maximum in 1–2 min, then gradually returned to control levels. Changes in CSFP were always associated with statistically significant decreases in arterial blood pressure and cerebral perfusion pressure, whereas the heart rate showed significant increases. Nicardipine may increase CSFP to undesirable levels in patients with intracranial hypertension.

Key Words: BRAIN—cerebrospinal fluid pressure, intracranial pressure. PHARMACOLOGY—calcium channel blockers, nicardipine.

Calcium channel blockers have potent vasodilating actions and are effective in the treatment of cerebral or coronary vasospasm (1–5). Recent animal experiments have suggested that calcium channel blockers may be promising agents in cerebral resuscitation (6,7). It seems that they will gain widespread use in clinical practices, including anesthesia (8–10), in the near future. Apart from their many beneficial effects, however, they have been reported to increase intracranial pressure in animals and humans (11–14), which might limit their clinical applicability. As far as we are aware, there have been few controlled studies concerning the effects of calcium channel blockers upon intracranial pressure in humans (10). The present study was thus undertaken to investigate the effects of nicardipine hydrochloride (1,4-dihydropyridine derivative), a water soluble and light insensitive calcium channel blocker, upon cerebrospinal fluid pressure (CSFP) in surgical patients without intracranial pathology.

Methods

The study was approved by the Institutional Human Studies Committee of Sapporo Medical College. Informed consent was obtained from each patient. Forty-seven adult patients (29 women, 18 men), ranging in age from 22 to 69 yr, who were scheduled to have spinal anesthesia for their surgical procedure, were selected for this study. No patient had any neurologic or cardiopulmonary disorders. All patients were premedicated with an intramuscular injection of hydroxyzine, 100 mg, and atropine, 0.5 mg, 1 hr before arrival in the operating room. A 16-gauge intravenous catheter was placed for infusion of lactated Ringer's solution and for drug administration. A 20-gauge catheter was inserted into the radial artery for continuous measurement of arterial blood pressure and for sampling arterial blood for blood gas analyses. After sterilizing and draping of the lumbar region, the patient lying in the lateral position, a 22-gauge spinal needle was introduced into the space between the third and fourth lumbar vertebrae. Upon demonstration of the free flow of clear cerebrospinal fluid, the needle was connected with a low compliance catheter to a transducer (p-50, Gould, USA) for continuous measurement of CSFP. The inside of the catheter was filled with sterile normal saline solution so as not to

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Address correspondence to Dr. Nishikawa, Department of Anesthesiology, Sapporo Medical College and Hospital, South-1, West-16, Chuoku, Sapporo, Hokkaido 060 Japan.

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Table 1. Patient Characteristics and Arterial Blood Gas Tensions before and after Nicardipine.

	Group 1	Group 2	Group 3
Number of patients	17	17	13
Sex (female/male)	10/7	11/6	8/5
Dose of nicardipine (mg/kg)	0.01	0.02	0.03
Age (yr)	48.1 ± 10.8	47.5 ± 13.7	46.3 ± 15.8
Height (cm)	156.9 ± 8.8	157.8 ± 8.7	157.8 ± 8.9
Body weight (kg)	58.1 ± 11.3	56.7 ± 7.9	57.8 ± 10.6
pHa			
before	7.39 ± 0.02	7.40 ± 0.02	7.41 ± 0.02
after	7.39 ± 0.03	7.40 ± 0.02	7.40 ± 0.02
Paco$_2$ (mm Hg)			
before	37 ± 4	37 ± 3	34 ± 3
after	37 ± 4	37 ± 3	35 ± 5
Pao$_2$ (mm Hg)			
before	88 ± 8	90 ± 8	92 ± 11
after	86 ± 9	90 ± 8	89 ± 11
BE (mEq/L)			
before	−2.2 ± 1.7	−1.6 ± 2.0	−2.5 ± 1.4
after	−1.8 ± 1.4	−1.7 ± 2.0	−2.4 ± 1.8

All values are mean ± SD.

remove cerebrospinal fluid, and care was taken to avoid introduction of air bubbles into the line. The midline of the vertebral column was taken as zero level. Thereafter, with the patient lying in the lateral position, ECG, arterial blood pressure, and CSFP were continuously recorded on a polygraph system (Nihon-Kohden, Tokyo) throughout the study.

Patients were randomly assigned to one of the following three groups according to the dosage of nicardipine: group 1 (0.01 mg/kg, $n = 17$), group 2 (0.02 mg/kg, $n = 17$), group 3 (0.03 mg/kg, $n = 13$). After the intravenous injection of nicardipine as a bolus, ECG, mean arterial pressure, mean CSFP, and heart rate were continuously recorded for 15 min. Arterial blood samples were obtained before and 15 min after the administration of nicardipine for measurement of pHa, Paco$_2$, Pao$_2$, and BE by Acid Base Laboratory 3 (Radiometer, Copenhagen). Cerebral perfusion pressure was calculated from the difference between mean arterial blood pressure and mean CSFP.

Data were expressed as mean ± SD. Data within groups were compared using Student's *t*-test for paired data. Data between groups were compared by analysis of variance and Student's *t*-test for unpaired data. $P < 0.01$ was considered statistically significant.

Results

Age, height, weight, and values of arterial blood analyses were comparable in all the three groups (Table 1). There were also no significant differences among the three groups in the mean control values of mean arterial blood pressure, heart rate, mean CSFP, and cerebral perfusion pressure.

Nicardipine, in doses of 0.01 mg/kg, 0.02 mg/kg, and 0.03 mg/kg increased CSFP in every patient (Fig. 1). An increase in CSFP occurred almost simultaneously with changes in blood pressure and heart rate, which attained the maximal changes in approximately 1–2 min after the injection of nicardipine, then gradually returned to the control values in 15 minutes (Fig. 1). CSFP levels after nicardipine increased to levels significantly above control values (Table 2). Mean arterial blood pressure and cerebral perfusion pressure also significantly decreased below the control values, as did the heart rate increase above control levels (Table 2). Maximal changes in mean CSFP after nicardipine in doses of 0.01 mg/kg, 0.02 mg/kg, and 0.03 mg/kg were 158 ± 31%, 189 ± 61%, and 226 ± 107%, respectively. However, there were no statistically significant differences after nicardipine among the three groups in CSFP or in other variables, although changes in CSFP seemed to be greater in dose-dependent manner. No significant change from control values was observed in arterial blood gas tensions after nicardipine in any of the three groups. There were no adverse reactions to nicardipine (headache, facial flushing, severe hypotension) in any of the patients.

Discussion

In this study, nicardipine hydrochloride as an intravenous bolus injection in doses of 0.01–0.03 mg/kg increased CSFP consistently in awake patients with

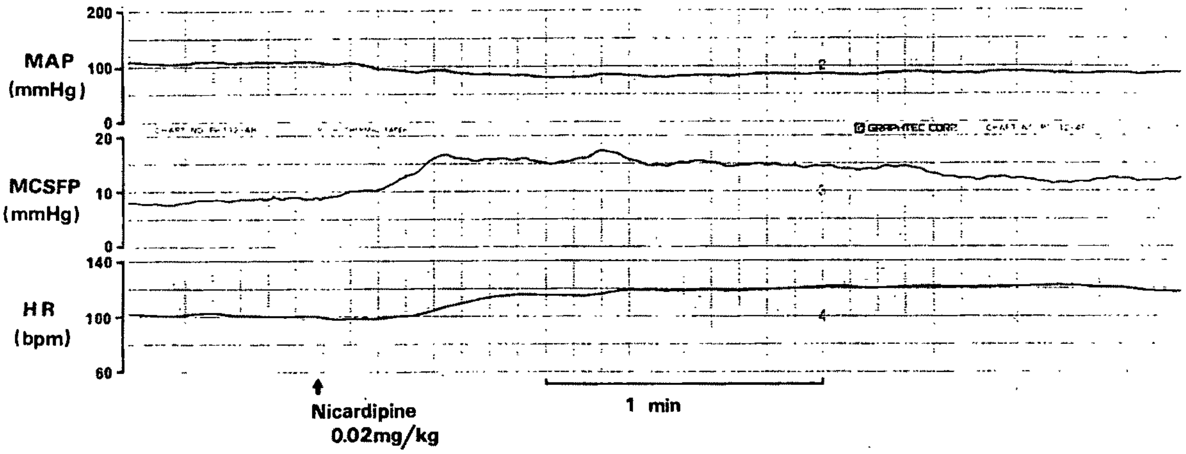

Figure 1. Representative polygraph tracings of mean arterial blood pressure (MAP), mean cerebrospinal fluid pressure (MCSFP), and heart rate (HR) after 0.02 mg/kg nicardipine as a bolus.

Table 2. Control Values of Mean Arterial Blood Pressure (MAP), Heart Rate (HR), Mean Cerebrospinal Fluid Pressure (CSFP), and Cerebral Perfusion Pressure (CPP) and Values during Maximal Changes after Nicardipine

	Group 1 (Nicardipine, 0.01 mg/kg)	Group 2 (Nicardipine, 0.02 mg/kg)	Group 3 (Nicardipine, 0.03 mg/kg)
MAP (mm Hg)			
Control	105.0 ± 15.6	104.1 ± 14.0	103.0 ± 12.9
Maximal changes	87.0 ± 12.6[a]	80.0 ± 9.3[a]	78.8 ± 12.4[a]
HR (beats/min)			
Control	86.5 ± 14.8	88.4 ± 18.3	87.9 ± 18.7
Maximal changes	102.4 ± 15.8[a]	109.0 ± 19.6[a]	108.0 ± 22.1[a]
CSFP (mm Hg)			
Control	7.6 ± 2.8	7.2 ± 3.4	7.4 ± 4.3
Maximal changes	11.6 ± 3.5[a]	12.2 ± 4.2[a]	13.8 ± 5.6[a]
CPP (mm Hg)			
Control	97.3 ± 15.1	96.9 ± 13.8	95.6 ± 12.1
Maximal changes	75.4 ± 12.6[a]	67.7 ± 9.3[a]	65.0 ± 12.5[a]

All values are mean ± SD.
[a] $P < 0.001$ compared to control values.

no intracranial lesions. Although CSFP levels after nicardipine were statistically significant, these increases were not clinically significant. These changes were always accompanied by simultaneous decreases in arterial blood pressure, which resulted in reductions of cerebral perfusion pressure. However, we observed no case of cerebral perfusion pressure less than 40 mm Hg, a critical level for development of cerebral ischemia. Heart rate increased after nicardipine in all subjects. Presumably this positive chronotropic effect may be mediated by baroreceptors secondary to systemic vasodilation.

It has been suggested that nicardipine may be approximately 100 times more potent as a cerebral vasodilator than papaverine, and its duration is more prolonged, e.g., about 30 min for 0.01 mg/kg intravenously (12). In anesthetized dogs, nicardipine increased both CSFP and cortical cerebral blood flow (12). The effect of nicardipine on CSFP has therefore been attributed to an increase in intracranial blood volume resulting from an increase in cerebral blood flow (12).

Nicardipine has cerebro- and cardiovascular actions similar to those associated with nifedipine in that both agents act mainly on the peripheral vessels, especially arterioles, and only little upon atrioventricular conduction (10,15). According to the report by Giffin et al. (11), nifedipine-induced hypotension in anesthetized cats increased intracranial pressure, but the increase was less than the increase in CSFP seen in our study, despite the fact that the reduction in mean arterial blood pressure was more pronounced in their experiments (55–65% of control values) than in ours (76–83%). This difference might be attributed to the mode of action of the calcium antagonist given, the method of its administration (continuous infusion vs bolus), and species (cats vs humans). Moreover, pentobarbital as an induction agent might have attenuated the effect of nifedipine on intracranial pressure in their study.

It is well-known that vasodilators such as nitroglycerin or nitroprusside produce marked increases in intracranial pressure (16–20). Nicardipine also increased CSFP, though nicardipine appears to be less potent in provoking an increase in CSFP for a given decrease in mean arterial blood pressure than has previously been reported for nitroglycerin (20). This might be explained by the fact that nitroglycerin, not a calcium channel blocker, acts more strongly on capacitance vessels (11,12,21).

In conclusion, calcium channel blockers given for purposes of correcting vasospasm or treating other cardiovascular disorders do not cause clinically significant increases in CSFP or harmful sequellae in the absence of intracranial pathology. However, the present data suggest that it might be prudent to avoid calcium channel blockers in patients with intracranial hypertension. Further investigation is necessary to determine whether the effects of calcium channel blockers on CSFP can be altered by changing either the method of administration (19), arterial carbon dioxide tension, or volatile anesthetics.

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Evaluation of Lidocaine as an Adjunct to Fentanyl Anesthesia for Coronary Artery Bypass Graft Surgery

Gregory W. Kasten, MD, and Eddie Owens, MD

KASTEN GW, OWENS E. Evaluation of lidocaine as an adjunct to fentanyl anesthesia for coronary artery bypass graft surgery. Anesth Analg 1986;65:511–5.

A double-blind, randomized, prospective trial was conducted to evaluate intravenous lidocaine, 3 mg/kg, followed by an infusion of 0.05 mg·kg^{-1}·min^{-1}, as an adjunct to fentanyl in 20 patients undergoing coronary artery bypass graft surgery. Lidocaine prevented hemodynamic abnormalities during tracheal intubation and after skin incision, but was ineffective in preventing hypertension following sternotomy. Intravenous lidocaine, 3 mg/kg, produced a decrease in mean arterial pressure after fentanyl, 30 μg/kg, that was unacceptable in some patients. Total fentanyl requirements for the duration of surgery were similar in the control group and in patients given lidocaine. We conclude that lidocaine, when administered as an adjunct to fentanyl in the dosage used in this study, can cause cardiovascular depression, and is of minimal benefit in preventing hemodynamic abnormalities after sternotomy during coronary artery bypass graft surgery.

Key Words: ANESTHETICS, LOCAL—lidocaine. ANESTHESIA—cardiovascular.

High-dose narcotic anesthesia is a common anesthetic technique for patients undergoing coronary artery bypass graft (CABG) surgery. However, several recent studies have documented that fentanyl alone may not always provide complete anesthesia for this procedure. Fentanyl (50–100 μg/kg) only incompletely suppresses hemodynamic responses to intubation and sternotomy (1,2) and does not always prevent intraoperative recall (3,4).

Numerous studies have evaluated diazepam, nitrous oxide, potent inhalational agents, and nitroglycerin as means to supplement fentanyl anesthesia to prevent the above problems. However, when halothane, diazepam, or nitrous oxide are combined with narcotic anesthesia, increased myocardial depression has limited their usefulness (5–8). The results of recent studies examining the effectiveness of nitroglycerin in preventing myocardial ischemia when used with fentanyl were conflicting (9,10).

Intravenous lidocaine blunts the increase in heart rate and blood pressure associated with laryngoscopy and tracheal intubation, and has been shown to decrease the minimum alveolar concentration of inhalation anesthetics (11–13); lidocaine may be superior to morphine as a supplement to nitrous oxide and diazepam for cardiac surgery (14). These beneficial hemodynamic and general anesthetic properties of lidocaine suggested its possible usefulness as a supplement to fentanyl for cardiac surgery. Our study evaluated lidocaine as a supplement to fentanyl for CABG surgery.

Methods

Twenty patients scheduled for elective CABG surgery were assigned to one of two treatment groups in a randomized double blind trial. Group F ($n = 10$) received fentanyl alone; group FL ($n = 10$) received fentanyl and lidocaine. The study was approved by the Human Investigations Committee, and all patients gave written informed consent. Patients were selected according to the following criteria: 1) adult male; 2) 45–65 yr old; 3) weight 60–100 kg; 4) angiographically proven coronary artery disease; and 5) currently receiving a β-blocking drug. Criteria for exclusion from the study were: 1) left main coronary artery disease; 2) ejection fraction of less than 45%; 3) type II or III atrioventricular block; 4) active seizure disorder; 5) lidocaine allergy; 6) hepatic disease; or 7) cimetidine therapy. The patients were block randomized into two groups upon entrance to the study according to these criteria: 1) age less than or greater

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Address correspondence to Dr. Kasten, Department of Anesthesiology, University of Kentucky Medical Center, Lexington, KY 40536-0084.

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Table 1. Patient Data[a]

	Fentanyl[b]	Fentanyl and lidocaine[b]
Age (yr)	55.1 ± 6.0	58.1 ± 6.3
Weight (kg)	74.7 ± 5.9	76.8 ± 8.9
Vessels grafted (#)	3.5 ± 0.7	3.8 ± 0.9
Ejection fraction (%)	59.0 ± 8.8	60.7 ± 7.8

No significant differences between the two groups ($P > 0.05$).
[a] Mean ± SD.
[b] $n = 10$.

than 55 yr, and 2) ejection fraction less than or greater than 60%.

Cardiac medications including nitrates, calcium channel blockers, and β-blockers were given the morning of surgery. Premedication included morphine sulfate, 0.12 mg/kg, and lorazepam, 2 mg, both given intramuscularly 45 min before surgery. Electrocardiogram leads were placed to continuously display the MCR_5 lead to monitor for myocardial ischemia. Invasive monitoring included arterial and central venous pressure catheters.

After the patients had been breathing oxygen, anesthesia was induced with fentanyl at a rate of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ until 30 μg/kg had been given. Pancuronium bromide, 2 mg intravenously, was administered after fentanyl, 5 μg/kg, had been given. After the patient had lost consciousness during the administration of fentanyl, additional pancuronium bromide, 0.15 mg/kg, was administered intravenously. The patient was then given the contents of a coded syringe containing either 3 mg/kg of lidocaine or normal saline solution. Tracheal intubation was performed 2 min later. After intubation, an intravenous infusion was started using a coded bottle containing either lidocaine at 0.05 $mg \cdot kg^{-1} \cdot min^{-1}$ or normal saline. The infusion was continued until cardiopulmonary bypass (CPB) was instituted and then restarted after conclusion of CPB when the patient was hemodynamically stable.

Mean arterial pressure (MAP), systolic pressure, diastolic pressure, heart rate, and central venous pressure (CVP) were recorded throughout the anesthesia at consistent intervals and before and after fentanyl and lidocaine administration, intubation, skin incision, and sternotomy.

Intravenous fentanyl, 5 μg/kg, was given when the patient responded to stress stimuli with an increase of at least 10 mm Hg MAP or an increase in heart rate of 5 beats/min above prestress values. An additional 5 μg/kg of fentanyl was given intravenously after 3 min if the hemodynamic variables did not respond to the initial dose. If there was no response 3 min after the second dose of fentanyl, nitroglycerin infusion (1–2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and 0.25–0.5% inspired concentration of isoflurane were administered. Isoflurane and nitroglycerin were discontinued upon return of the hemodynamic parameters to baseline. This sequence was repeated each time the hemodynamic variables increased by the previously defined amounts.

Blood samples were drawn from five patients receiving lidocaine and from five control patients not receiving lidocaine (to prevent unblinding of the study) from the CVP line at the following times: 2 and 5 min after the bolus; 15 and 30 min after the infusion began; 1 min prior to CPB; 2, 5, and 10 min after CPB began; 1 min prior to CPB termination; and 2, 5, and 30 min after termination of CPB. After centrifugation, serum levels of lidocaine were measured by fluorescence polarization immunoassay with a lower detection limit of 0.01 μg/ml.

Data were analyzed using Student's *t*-test for paired and unpaired data, and analysis of variance. A probability level of $P < 0.05$ was considered statistically significant. Data are presented as mean ± SD.

Results

There were no significant differences between group F (fentanyl) and group FL (fentanyl + lidocaine) with regard to age, weight, number of vessels grafted, or ejection fraction (Table 1). Preoperative use of nitrates, calcium channel blockers, and digoxin was similar in both groups. The dose of β-blockers was similar in both groups, ranging from 80–400 mg/day of propranolol and from 50–150 mg/day of metoprolol.

Administration of lidocaine after fentanyl, 30 μg/kg, resulted in a significant decrease in MAP and rate pressure product (RPP) below baseline levels both before and after intubation (Table 2). The decrease was drastic enough (MAP less than 60 mm Hg) in three patients to require administration of small doses of ephedrine (5–10 mg) intravenously to restore MAP to an acceptable level. Lidocaine also caused a significant decrease in MAP and RPP below baseline levels both before and after skin incision and a significant decrease in MAP just prior to sternotomy.

The only significant differences in MAP between the two groups of patients were before and after intubation, with no significant differences between the groups at any other time during the study. The responses to sternotomy were similar in both groups. Five minutes after sternotomy, MAP and RPP were significantly increased above control in both groups (Figs. 1 and 2). A significant increase in heart rate above baseline levels occurred in group F 1 min after sternotomy and in both groups 5 min after sterno-

Table 2. Hemodynamic Results during Anesthesia and Surgery

	Baseline	After fentanyl	After lidocaine	Before intubation	After intubation	Before skin incision	After skin incision	Before sternotomy	After sternotomy (1 min)	After sternotomy (5 min)
RPP										
Fentanyl	8210 ± 1480	7840 ± 1250^a	7890 ± 1615^a	7460 ± 1505	8130 ± 1415	7445 ± 1316	7980 ± 1205	7750 ± 1350	9815^a ± 1710	10,400^a ± 2180
Fentanyl and lidocaine	8470 ± 1720	8240 ± 1810^a	7405 ± 1460^a	7330 ± 2105^a	7490 ± 1110^a	7580 ± 1410^a	7610^a ± 1360	7810 ± 1915	9690 ± 1975	10,810^a ± 2710
Heart rate										
Fentanyl	59.7 ± 3.2	59.0 ± 3.0	60.1 ± 3.2	60.1 ± 5.6	65.1 ± 6.9	65.1 ± 6.9	60.6 ± 8.3	61.9 ± 7.3	65.2^a ± 7.1	65.4^a ± 6.9
Fentanyl and lidocaine	62.3 ± 4.9	62.5 ± 4.8	65.2 ± 6.7	60.6 ± 3.7	62.7 ± 5.4	62.7 ± 5.4	62.2 ± 4.2	61.7 ± 4.4	62.8 ± 4.2	65.5^a ± 4.6
MAP										
Fentanyl	92.5 ± 11.8	89.5 ± 15.0	89.7 ± 13.7	90.1 ± 13.9	95.1 ± 12.1	88.7 ± 11.6^a	93.2 ± 13.5	91.9 ± 10.8	108.5 ± 18.9^a	115.6 ± 17.8^a
Fentanyl and lidocaine	93.7 ± 7.5	91.2 ± 10.6	79.5 ± 16.5^a	78.9 ± 17.0^{a,b}	81.1 ± 15.4^{a,b}	86.5 ± 11.1^a	88.5 ± 12.3^a	88.1 ± 11.9^a	99.2 ± 17.2	110.6^a ± 16.4

Abbreviations: RPP, rate pressure product; MAP, mean arterial pressure.
$^a P < 0.05$ compared to baseline.
$^b P < 0.05$ between groups.

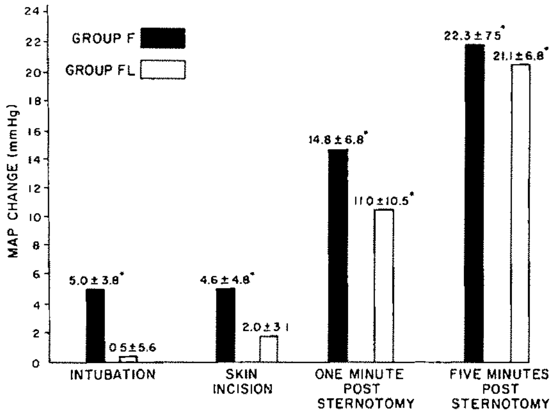

Figure 1. Changes (mean ± SD) in mean arterial pressure (MAP) 1 min after intubation, 1 min after skin incision, 1 min after sternotomy and 5 min after sternotomy from levels 30 sec prior to the event. Asterisk denotes $P < 0.05$ as compared to the immediately preceding value.

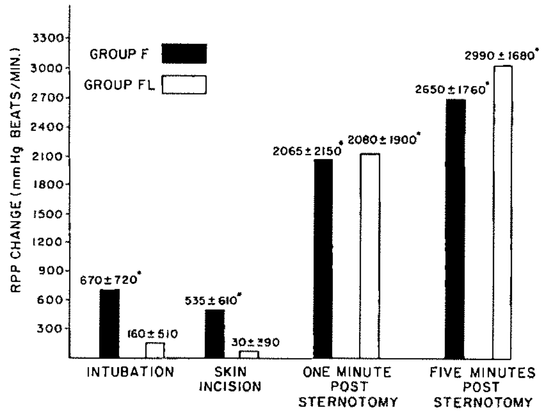

Figure 2. Increases in rate pressure product (RPP) one min after intubation, 1 min after skin incision, and 1 and 5 min after sternotomy from values 30 sec prior to the event. Asterisk denotes $P < 0.05$ as compared to the immediately preceding value.

tomy. In both group F and group FL, a significant increase in heart rate was found 30 min after CPB; there were no significant differences in hemodynamics between the two groups during or after CPB. Three patients in each group developed ECG evidence of myocardial ischemia (>1 mm ST depression in V_5) before initiation of CPB; treatment was with nitroglycerin.

Differences in requirements for incremental fentanyl dosage, nitroglycerin, and isoflurane were significant between the two groups only after the skin incision. Total fentanyl requirements did not differ in the two groups: group F, 58.0 ± 13.7 μg/kg; group FL, 55.0 ± 15.7 μg/kg. The fentanyl dosage averaged 45.4 ± 6.9 μg/kg in patients with ejection fractions of 45–60% and 64.4 ± 7.4 μg/kg in patients with ejection fractions of 61–75% ($P < 0.01$).

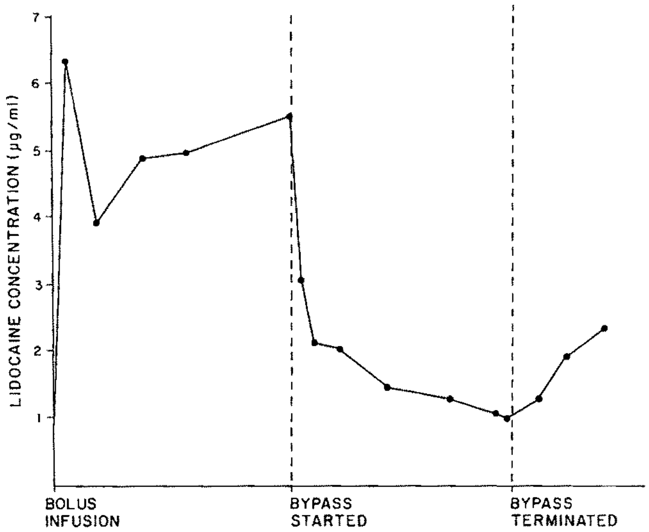

Figure 3. Lidocaine serum concentrations (mean values) in the five patients. Each data point corresponds to the time of serum sampling described in text. The vertical dashed lines indicate onset and termination of cardiopulmonary bypass.

Lidocaine serum levels are shown in Figure 3. The initiation of CPB resulted in a significant decrease in lidocaine serum levels from 5.4 ± 2.5 μg/ml 1 min before bypass to 3.0 ± 1.0 μg/ml 2 min after initiation of bypass. The total lidocaine dose for the duration of the procedure was 851 ± 160 mg.

Discussion

Lidocaine was only minimally effective in preventing adverse hemodynamic responses after stressful stimuli during CABG surgery. Lidocaine was beneficial during tracheal intubation and skin incision, but hemodynamic responses to sternotomy were unchanged. During the intense stressful stimulus of sternotomy (15), the hemodynamic responses and the need for fentanyl, nitroglycerin, and isoflurane were similar with or without intravenous lidocaine.

The mild beneficial hemodynamic advantages obtained with adjunctive lidocaine administration during intubation and skin incision were offset by a consistent decrease in MAP after lidocaine administration. Three patients required intravenous ephedrine to restore blood pressure to an acceptable (90 mm Hg systolic) level. The hypotension associated with lidocaine appears to be similar to that seen when diazepam is given with fentanyl (7).

Several mechanisms could explain the cardiovascular depression caused by lidocaine administered after intravenous fentanyl, including the decreases in cardiac contractility and stroke volume seen in animals, normal subjects, and patients with coronary artery disease (16,17). Lidocaine has also been shown to be additive to propranolol in producing myocardial depression (17). In our investigation, patients had coronary artery disease and were receiving β-blockade therapy; thus, they were likely candidates for additional myocardial depression due to lidocaine. A critically ill patient with decreased myocardial reserve may develop an even greater cardiovascular depression after lidocaine administration, which could be detrimental.

Several studies have demonstrated a general anesthetic-like effect of lidocaine. Lidocaine at serum concentrations of 1.1–5.5 μg/ml decreases the MAC of nitrous oxide in humans (12), the MAC of enflurane and halothane in dogs (12,13), and the MAC of cyclopropane in rats (18). The serum levels in these reports are similar to those observed in this study. Despite this general anesthetic-like effect of lidocaine, we did not find a significant reduction in total fentanyl requirements.

In summary, lidocaine is of limited effectiveness in protecting against many of the hemodynamic changes that occur during CABG surgery, and it does not decrease fentanyl requirements. Lidocaine did have modest beneficial hemodynamic effects during intubation and skin incision, but these were offset by the hypotension that occurred after fentanyl, 30 μg/kg, in some patients. This study does not support the usefulness of lidocaine as a supplement to fentanyl anesthesia during CABG surgery.

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Clinical Reports

Anesthetic Management of Patients Undergoing Fontan Procedure

Phillip N. Fyman, MD, Kenneth Goodman, MD, Pierre A. Casthely, MD,
Randall B. Griepp, MD, M. Arisan Ergin, MD, and Patricia Smith, SNA

Major advances in surgical and anesthetic techniques have permitted critically ill patients to undergo surgical correction of complex congenital cardiac defects that were previously inoperable. Rodband and Wagner (1) performed the first experimental right ventricular bypass. Later, Glenn demonstrated that a right heart bypass could be successfully performed in humans by anastomosing the superior vena cava to the right pulmonary artery (2). This demonstrated for the first time that satisfactory pulmonary perfusion could be obtained with venous blood pressure. In 1971 the first successful case of total venous diversion was reported by Fontan and Baudet (3). The superior vena cava was anastomosed to the distal right pulmonary artery, and an aortic homograft was used to anastomose the right atrial appendage to the proximal right pulmonary artery. The Fontan procedure was initially developed for patients with tricuspid atresia. Because of the favorable outcome, indications for this procedure were expanded to include more complex cardiac lesions. Among these are transposition of the great vessels with a univentricular heart, pulmonary artery atresia or both. Although the surgical techniques for the Fontan procedure have been described in detail (3–8), there are no reports describing anesthetic management. Safe and effective management of these patients during the perioperative period requires appreciation of the pathological changes that occur before and after surgical repair. In this report, we review our anesthetic management of eight patients with various cardiac deformities who underwent the Fontan procedure.

Methods

From December 1982 through June 1985 eight patients underwent the Fontan procedure at our institution. Patients included four males and four females with ages ranging from 4 to 26 yr (with a mean of 13) and a mean weight of 38 ± 9.6 kg (Table 1). Preoperative diagnoses included two cases of transposition of great vessels (TGV) and tricuspid atresia, two cases of TGV and a single ventricle, with one having pulmonic stenosis, three cases of tricuspid atresia, one of whom also had pulmonary atresia, and one patient with TGV, tricuspid atresia and pulmonic stenosis. Six of the eight had undergone palliative procedures in the past, including Glenn shunts (three), pulmonary artery banding (one), Cooley procedure (one), and Potts and B-T shunt (one). Preoperatively all patients had normal pulmonary vascular resistance (PVR), 1.1 ± 0.2 units (± SEM), and normal-sized pulmonary arteries. In one patient the pulmonary artery pressures were increased, but the increases were thought to be secondary to high flow. Calculated PVR was normal, and lung biopsies done 9 months earlier (at the time of pulmonary artery banding) showed no evidence of vascular changes. Preoperative arterial blood gas measurements (ABGs) done while patients breathed room air demonstrated significant hypoxia in all patients. Mean pH was 7.39 ± 0.01, P_{CO_2} was 25 ± 3.1, and P_{O_2} was 50 ± 1.3 mm Hg (± SEM, Table 2). Preoperatively all patients were in New York Heart Association (NYHA) Class III or IV. Five patients were taking digitalis and diuretics.

On the day of the surgery patients were premedicated with meperidine, 1 mg/kg, or morphine, 0.1 mg/kg, intramuscularly, and/or diazepam, 2.5–5.0 mg orally approximately 90 min before being brought to the operating room. Patients who would tolerate intravenous catheterization were catheterized at that time. Adults had arterial and central venous cannulae

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Address correspondence to Dr. Fyman, Department of Anesthesiology, Long Island Jewish-Hillside Medical Center, 270-05 76th Avenue, New Hyde Park, NY 11040.

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Table 1. Patient Characteristics

Patient number	Age (yr)	Weight (kg)	Sex	Congenital defect(s)	NYHA Class
1	6	14.6	M	L-TGV, SV	Died 24 hr postoperatively
2	4	12	F	TGV, PS, SV	I–II
3	17	79.5	F	TGV, TA	III
4	19	52	F	TA	I–II
5	26	71	M	L-TGV, TA, PS	I–II
6	7	20	M	TA, PA	II
7	5	14	M	TA	I–II
8	23	43.6	F	TGV, TA	II

Abbreviations: TGV, Transposition of great vessels; SV, single ventricle; PS, pulmonic stenosis; TA, tricuspid atresia; PA, pulmonary artery atresia; NYHA Class, New York Heart Association Class, postoperatively.

inserted under local anesthesia while breathing 100% oxygen. In patients with an intravenous catheter in place, anesthesia was induced with fentanyl, 20–50 μg/kg, over 5–10 min. Tracheal intubation was facilitated with pancuronium, 0.15 mg/kg. In younger patients without an intravenous catheter in place, anesthesia was induced with halothane, 1–1.5%, in 100% oxygen. When an adequate plane of anesthesia had been achieved, arterial, peripheral, and central venous lines were inserted. The distal tip of the central venous pressure (CVP) catheter was located in the superior vena cava or innominate vein, which was confirmed by palpation prior to institution of cardiopulmonary bypass (CPB). Pancuronium was administered in the dose noted above, and tracheal intubation was accomplished. Halothane was then discontinued, and fentanyl, 10–30 μg/kg, was administered over 10–20 min. Induction of general anesthesia was well-tolerated with minimal changes in blood pressure and heart rate. Patients were ventilated using volume ventilators with tidal volume and rate set to maintain normocarbia. Peak airway pressure was kept below 15 cm of water pressure. Arterial blood gas tensions after induction of general anesthesia showed a mean pH of 7.38 ± 0.02, P_{CO_2} of 31.6 ± 2.3, and a P_{O_2} of 102 ± 21 (± SEM), with P_{O_2} ranging from 48 to 241 mm Hg. After CPB, the mean pH was 7.39 ± 0.04, P_{CO_2} 35.9 ± 3.5 and P_{O_2} 281 ± 61 mm Hg (± SEM). The ABGs before and after CPB were essentially unchanged except for the marked increase in P_{O_2}.

Surgical correction was accomplished by creation of direct anastomosis between the right atrium and the pulmonary artery. No conduits were used. A pericardial patch was used to enlarge the anastomosis. Cold cardioplegia and systemic hypothermia of 20°C were used. Duration of CPB ranged from 80 to 225 min with a mean of 125 ± 16 min (± SEM). After CPB, systemic blood pressure was 85–110 mm Hg systolic, mean right arterial pressure and pulmonary artery pressures were between 16 and 18 mm Hg, and left atrial pressure was 7–10 mm Hg. Patients were transferred to the intensive care unit with left atrial catheter in place to facilitate postoperative care. Ringer's lactate solution, dopamine (3–5 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$), and sodium nitroprusside (0.5-1 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$) were administered as needed to maintain adequate cardiac output. All patients remained in normal sinus rhythm after CPB. Six of eight patients required dopamine and sodium nitroprusside infusion before they left the operating room, and these drugs were continued for 1–2 days because of low cardiac output.

Of the seven patients who survived, five were extubated on the first postoperative day, and one on the second. The seventh patient was resuscitated after a cardiac arrest that was precipitated by a respiratory event. Because of resulting neurologic damage, prolonged mechanical ventilation was required, necessitating a tracheostomy. All surviving patients developed pleural effusions postoperatively. Two did not respond to digitalization and diuretics and required thoracentesis. Six patients are now classified as NYHA Class I or II, while one remains a Class III. Digitalis therapy was begun in all patients prior to hospital discharge.

The eighth patient, a child with L-TGV and a single ventricle, died 24 hr postoperatively after an uneventful intraoperative course. Six hr postoperatively, PVR increased, as evidenced by increases in right atrial pressure and pulmonary artery pressure to 28 mm Hg. Left arterial pressure remained in the 10–12 mm Hg range. Progressive hypoxia with severe metabolic acidosis developed and was associated with a decrease in mixed venous P_{O_2} to 23 mm Hg from 55 mm Hg. This low-output syndrome was refractory to various combinations of dopamine, sodium nitroprusside, isoproterenol, and epinephrine, in addition to intermittent boluses of sodium bicarbonate. The cause of pulmonary vasoconstriction was not determined. This patient had undergone pulmonary artery band-

Table 2. Perioperative Arterial Blood Gases

	pH	P_{CO_2}	P_{O_2}
Preoperative ($F_{I_{O_2}}$ 0.2)	7.39 ± .01	35 ± 3.1	50 ± 1.3
Before CPB ($F_{I_{O_2}}$ 1.0)	7.38 ± .02	31 ± 2.3	102 ± 21
After CPB[a] ($F_{I_{O_2}}$ 1.0)	7.39 ± .04	36 ± 3.5	281 ± 61

Abbreviation: CPB, cardiopulmonary bypass.
[a] At the termination of surgery.

ing 6 months prior to the Fontan procedure, which reduced the pulmonary artery pressures. These pressures remained low for at least 2 months postoperatively, as assessed by a substantial gradient across the band on Doppler echocardiography. Immediately before undergoing definitive surgical correction, this gradient had disappeared and the pulmonary artery pressure was elevated, which was thought to be secondary to increased flow and not increased vascular resistance. At the time of surgery, the band was found to have eroded through the pulmonary artery and was within the lumen, but was not obstructing flow.

Discussion

The Glenn procedure was the first shunt used to effectively bypass obstruction of blood flow through the right ventricle. However, the Glenn procedure was never completely satisfactory because of complications such as cerebral edema and the development of ventilation perfusion abnormalities. In addition, as patients grew, the shunt became inadequate. Because of these shortcomings, the Fontan procedure was developed for patients who would benefit from surgical bypass of the right ventricle. This correction creates a direct atriopulmonary artery connection. Initially, the anastomosis was made using a conduit, with or without a valve. Because of serious complications with conduits, the anastomosis is now made directly. One potential complication is compression of the conduit by the sternum, obstructing flow. Another is peel formation. This complication occurs in tightly woven grafts when the newly formed endothelial lining does not adhere to the graft and "peels" off. This too can obstruct flow through the graft. Frequently a pericardial patch is used to permit formation of a wider anastomosis. Studies of long-term survivors of the Fontan procedure (9) have found that the beneficial hemodynamic results persist. Because of its success, and its adaptability to other complex congenital heart defects, such as TGV with a single ventricle or TGV and pulmonary atresia, indications for the Fontan procedure have been expanded beyond tricuspid atresia.

Despite the complex nature of the underlying cardiac abnormalities in our patients, all of them had a smooth intraoperative course. Hemodynamic stability was maintained, both in patients that had inhalation induction, as well as those that had a pure narcotic technique (4). After weaning from CPB, three quarters of the patients required dopamine and sodium nitroprusside because of right-sided heart failure. All but one responded well.

Immediately after CPB, and continuing into the early postoperative course, it is important to maintain moderately high mean right arterial pressure because the main pumping chamber, the right ventricle, has been eliminated from the pulmonary circuit. Under these circumstances the right arterial pressure serves as the pressure head to perfuse the pulmonary system. In this series of patients hemodynamic and metabolic status was usually optimal with a mean right arterial pressure in the 16–18 mm Hg range. Because the right atrium is not able to contact forcefully, the Fontan procedure is contraindicated in patients with a high PVR or a small pulmonary artery because adequate pulmonary perfusion would not occur.

After surgical correction, the right atrium assumes a major role in propelling blood into the lungs. Because the right atrium's contractility is much less than that of a normal ventricle, an increase in PVR can be expected to cause right-sided failure, which is a major cause of postoperative morbidity and mortality. Care must therefore be taken to avoid high peak airway pressure. One precaution is to avoid ventilator settings or maneuvers that will cause prolonged increases in duration of inspiration or increases in airway pressure. In our patients, peak airway pressure was kept at 15 cm H_2O or less. Other factors that could increase PVR were avoided, including "bucking" on the ventilator, hypothermia, hypercarbia, and acidosis. Of the seven surviving patients, five were extubated on the first postoperative day, which helped alleviate problems with mechanical ventilation that might lead to high PVR.

Positive inotropic drugs, vasodilators, or both were aggressively used at the first sign of low cardiac output as evidenced by decreasing blood pressure with increasing mean right atrial and pulmonary artery pressures, and by decreases in systemic blood pressures and mixed venous oxygen concentration. In our experience, when failure occurred, initially it involves the right side of the heart, never the left, based on the above parameters and low left atrial pressure. Patients responded well to an infusion of dopamine and sodium nitroprusside, the efficacy of which has been previously documented in these circumstances (10). Use of sodium nitroprusside can be crucial because it maintains low PVR and optimizes right heart function, permitting the right atrium to adapt to its new role. Furthermore, the dopamine–sodium nitroprusside combination will also help optimize left ventricular function, through inotropy and reduction of afterload, keeping left atrial pressure low. Pulmonary perfusion will be enhanced because of the favorable pressure gradient going from right to left atrium.

It is interesting to note that the only death in this series occurred in a 6-yr-old boy who developed acute pulmonary vasoconstriction 6 hr postoperatively, leading to severe right-sided failure. Nine months earlier he had had a lung biopsy performed during pulmonary artery banding. At that time there were no histologically demonstrable pulmonary vascular changes. Intraoperatively during the Fontan procedure this patient did well, with pulmonary artery and right arterial pressures of 18–20 mm Hg. There may be unidentifiable factors, such as increased autonomic system activity, that precipitate pulmonary vasoconstriction in some patients.

One patient required creation of a pericardial window 3 months after the Fontan procedure because of a persistent pericardial effusion. Not uncommonly, ascites and low extremity edema may appear almost immediately postoperatively but usually resolve within a few weeks. However, they can persist for months. These complications occur because high right atrial pressure impairs venous return. Fortunately, ascites and persistent lower extremity edema were not a problem in this series.

In summary, patients undergoing Fontan procedure respond well to general anesthesia with fentanyl or halothane. After CPB it is important to maximize pulmonary blood flow. It is also critical to monitor right atrial, pulmonary artery, and left atrial pressures to detect hemodynamic deterioration early. Maintaining right arterial pressure in the range of 16-20 mm Hg, observing patients closely for signs of increasing PVR, and aggressive treatment of elevation of PVR with appropriate pharmacologic agents, are also crucial. Early extubation is desirable. If pleural effusions do develop postoperatively, initial therapy should consist of digitalization and the administration of diuretics.

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Heparin-Associated Thrombocytopenia:

Alternative Managements

J. S. Vender, MD, E. B. Matthew, MD, I. M. Silverman, MD, H. Konowitz, MD, and P. C. Dau, MD

Heparin Associated Thrombocytopenia (HAT) is a well-described clinical entity (1–5), frequently requiring prompt cessation of heparin therapy to correct the thrombocytopenia. Previously recommended management also called for discontinuing heparin for several weeks to allow the alteration in platelet aggregation to normalize prior to the safe readministration of heparin. Discontinuation of heparin presents a challenging clinical problem in patients who have developed HAT and subsequently require urgent cardiac surgery. The case report describes the use of plasmapheresis to rapidly reverse the immunologic abnormality reportedly responsible for HAT, permitting the early use of heparin in a patient with HAT who required urgent cardiac surgery.

Case Report

A 50-yr-old man presented with an acute anterolateral myocardial infarction that resulted in cardiogenic shock refractory to medical therapy. Intraaortic balloon counterpulsation (IABP) was instituted, resulting in rapid hemodynamic improvement. Cardiac catheterization revealed a 100% occlusion of the left main coronary artery with a right dominant circulation, left ventricular hypokinesis, and a 40% ejection fraction. Urgent coronary artery bypass surgery was recommended.

Since the insertion of the IABP, the patient had been receiving porcine lung heparin by continuous intravenous infusion. After the initiation of heparin therapy, the platelet count progressively decreased, reaching a nadir of 31,000 after 8 days. Other coagulation studies were normal, and hematologic consultation was obtained. Initial in vitro heparin-stimulated platelet aggregation studies were positive, suggesting an abnormal, heparin-dependent, IgG platlet aggregation factor. A presumptive diagnosis of HAT was made, heparin was immediately discontinued, and a dextran infusion was begun to facilitate continued use of the IABP. The platelet count progressively increased to 180,000 3 days after discontinuation of heparin. However, platelet aggregation studies remained positive, indicating persistence of the abnormal IgG platelet aggregation factor (Fig. 1).

In an effort to reverse the platelet aggregation abnormality and to safely allow early use of heparin, plasmapheresis was begun. After the first plasmapheresis treatment, platelet aggregation studies became negative (i.e., normal) and remained negative thereafter. The patient had plasmapheresis on 5 consecutive days and received 35 g of immunoglobulin intravenously after the last treatment.

On the day after completion of plasmapheresis, 17 days after the myocardial infarction and 9 days after heparin was stopped, the patient underwent coronary artery bypass grafting surgery. After an uneventful induction of anesthesia with fentanyl, 75 μg/kg, a total of 44,000 units of heparin was administered intravenously to prevent anticoagulation during extracorporeal circulation. The activated clotting time remained greater than 600 sec throughout cardiopulmonary bypass, and the heparinization was reversed with protamine. The lowest postoperative platelet count was 180,000, and there was no significant postoperative bleeding. Postoperative platelet aggregation studies remained negative, and the patient was discharged 15 days after surgery without complications.

Discussion

The administration of heparin has been associated with thrombocytopenia in up to 30% of patients (1).

Received from the Departments of Anesthesiology and Medicine, Evanston Hospital, Evanston, Illinois and Northwestern University Medical School, Chicago, Illinois. Accepted for publication December 17, 1985.

Address correspondence to Dr. Vender, Department of Anesthesiology, Evanston Hospital, 2650 Ridge Avenue, Evanston, IL 60201.

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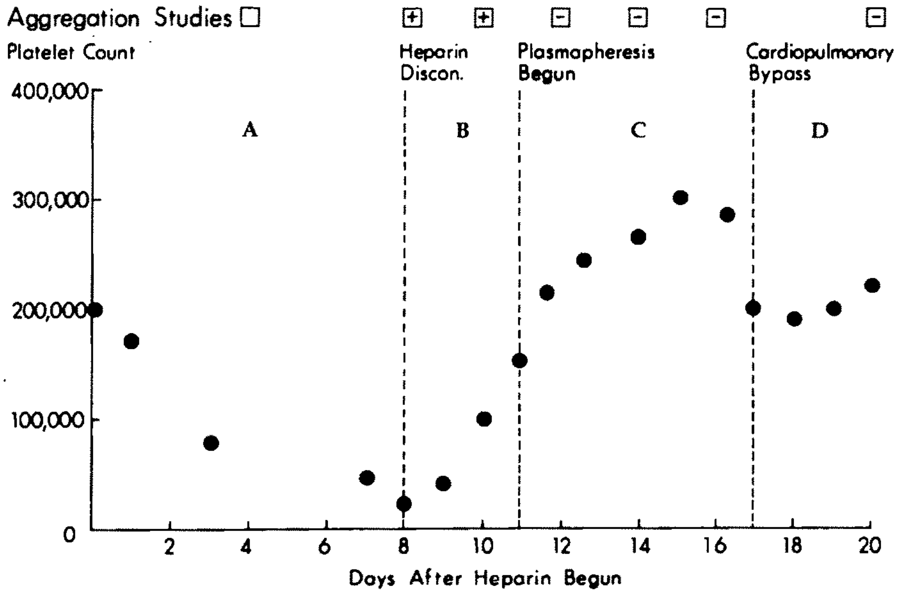

Figure 1. Platelet count and platelet aggregation study results after heparin. Platelet counts and platelet aggregation study results (A) after heparin was begun, (B) after heparin was discontinued, (C) after plasmapheresis was begun, and (D) after cardiopulmonary bypass. Positive platelet aggregation studies are abnormal. Note normalization of platelet aggregation studies after plasmapheresis.

Two classic patterns of HAT are described in the literature. A mild, benign form of thrombocytopenia is most common. The onset is within 1–2 days of the institution of heparin therapy, and platelet counts rarely decrease below 80,000 (2). There are no hemorrhagic or thrombotic complications, and no immunologic abnormality has been identified. A possible mechanism is reversible platelet aggregation, margination, and sequestration due to ADP release (3). This syndrome resolves spontaneously within 3–5 days, is usually of limited clinical significance, and requires no specific therapy.

A more severe form of HAT exists with an incidence of approximately 0.6% (4). This form occurs 7–14 days after initiation of heparin therapy and frequently presents with thrombotic or hemorrhagic phenomena, an increase in heparin requirements for maintenance of anticoagulation, and an associated thrombocytopenia. Platelet counts often decrease to below 50,000. Bone marrow biopsy results are either normal or reveal increased megakaryocytes consistent with peripheral platelet destruction (5).

An immunologic mechanism has been postulated to explain severe thrombocytopenia. Heparin may act as a hapten with platelet membranes, thus stimulating formation of a membrane antibody, which results in platelet aggregation (4). In vivo studies have isolated increased platelet-associated IgG and C_3 in affected patients (6). These patients have positive in vitro platelet aggregation studies, and the thrombocytopenia resolves when heparin is discontinued, further suggesting an immunologic mechanism.

The cornerstone of management of HAT is discontinuation of heparin until platelet aggregation studies become negative (i.e., normal) (7). This presents a potentially serious clinical problem when urgent cardiac surgery or other conditions requiring heparin therapy are indicated in patients who are recovering from HAT. The immunologic abnormality may resolve within 3–4 weeks after discontinuation of heparin, but positive aggregation studies have been reported for up to 12 months after the initial onset of HAT (3), indicating persistence of the abnormal, heparin-dependent, IgG platelet aggregation factor. Heparin rechallenge may induce massive platelet aggregation if the circulating IgG antibody is still present (8). Several management alternatives have been suggested for patients with HAT who require cardiac surgery. Delay of surgery until resolution of the abnormal platelet aggregation studies, although desirable, often is not practical due to the urgency of the situation. Warfarin could be used as an anticoagulant for cardiopulmonary bypass, but it is not easily reversible.

Pretreatment with platelet inhibitory drugs such as dipyridamole followed by heparin therapy while platelet aggregation studies are still positive has recently been reported (9). Although the patient managed in this way survived, postoperative thrombocytopenia was significant, and reexploration for cardiac tamponade was necessary 17 hr after surgery. Prostacycline analogs have been used for anticoagulation instead of heparin during hemodialysis (10) and as platelet inhibitors in patients with HAT receiving heparin anticoagulation during cardiopulmonary bypass (11). However these drugs may produce hypotension, caused by vasodilation.

We present the first case report of plasmapheresis and high-dose γ-globulin as an adjunct to management of a patient with HAT who required urgent cardiac surgery. Plasmapheresis has been described as a therapy for several clinical problems involving abnormal IgG antibody, such as myasthenia gravis and antiglomerular basement membrane disease (12). The goal of plasmapheresis is removal of abnormal plasma constituents, such as antibodies, by centrifuging the patient's blood, removing the plasma, and returning red blood cells plus colloid and crystalloid. Approximately 45% of the body's IgG is intravascular, thus making it immediately accessible for removal by plasmapheresis. The remainder of the IgG is in the interstitial fluid compartment and gradually reequilibrates with plasma over time. A series of five large-volume plasmaphereses is required to remove 90% or more of the antibody initially present. High-dose γ-globulin has been effective in increasing platelet counts in other syndromes presenting with thrombocytopenia, such as idiopathic thrombocytopenia purpura (13,14). A mechanism postulated to account for γ-globulin's effectiveness in increasing platelet counts is that IgG catabolism causes overload and blockade of the reticuloendothelial system, thereby reducing platelet clearance. In the present case, the combined therapy was used in an attempt to clear the abnormal, heparin-dependent, IgG platelet aggregation factor from the patient's plasma, promoting immediate conversion of the platelet aggregation studies from positive to negative, and to increase the platelet count. We thus hoped to obviate the need to wait several weeks for spontaneous resolution of the platelet aggregation abnormality before heparin could be administered for cardiopulmonary bypass.

Heparin-associated thrombocytopenia is an important clinical entity that may delay or complicate the administration of heparin for cardiac surgery. Plasmapheresis, followed by high-dose γ-globulin, enabled the rapid reversal of the platelet aggregation abnormality in the patient we report, and allowed early and uncomplicated heparinization for cardiac surgery. This therapy warrants further evaluation in the management of patients with HAT who require early readministration of heparin.

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Delayed Cephalad Spread of a Lidocaine Spinal Anesthetic Causing Ventilatory Failure

Bruce Kleinman, MD, and Ronald Belusko, MD, PhD

Spinal anesthesia, irrespective of the local anesthetic used, is a time-proven anesthetic technique that provides ideal operating conditions for lower abdominal and lower extremity operations. Various local anesthetics can be used to inject into the subarachnoid space. Tetracaine and lidocaine are the two most extensively used local anesthetics. Moore suggests that lidocaine should not be used because of a possible tendency for delayed cephalad spread (1). However, this suggestion is not supported by case reports or investigations. A search of the literature failed to reveal articles describing delayed cephalad spread of lidocaine used for spinal anesthesia to the extent that respiration was impaired. We report such a case.

Case Report

A 55-yr-old woman was scheduled for transurethral resection of a bladder tumor. Past medical history was unremarkable. The patient was 161 cm tall and weighed 81.3 kg. Physical examination was essentially normal.

The patient was taken to the operating room and, after applying appropriate monitors, we performed an atraumatic dural puncture with a 22-gauge spinal needle introduced in the L3–4 interspace with the patient in the left lateral decubitus position and the operating room table in the horizontal position. A hyperbaric solution of 1.6 ml consisting of 120 mg of 7.5% dextrose and 80 mg of 5% lidocaine was injected. The patient was then turned to the supine horizontal position. Level of pinprick analgesia was at T6 10 min after injection. At this time (10 min after injection), the patient was put into the lithotomy position and the operation proceeded uneventfully. Forty minutes after performance of the spinal anesthetic, the patient was taken to the recovery room. On admission to the recovery room she was conscious and alert, but she was complaining of dypsnea and was in obvious respiratory distress. The level of analgesia as tested by pinprick was above C5. Ventilation was assisted with bag and mask. Shortly thereafter, 300 mg of thiopental was administered intravenously; the patient was intubated and placed on mechanical ventilatory support. After 60 min of mechanical ventilation, the level of anesthesia receded to T10. After discontinuation of mechanical ventilation, when she met the criteria for extubation, she was safely extubated. Her subsequent postoperative course was unremarkable.

Discussion

The distribution of local anesthetic drugs in the subarachnoid space depends upon many factors, some of which are controllable by the anesthesiologist (2). Spread of drugs in spinal fluid is related to the difference in density between the cerebrospinal fluid and the local anesthetic (2). Volume of the local anesthetic is also important (3). Although not a linear relationship, the larger the volume injected, the greater the area anesthetized. Total dosage, relating volume and concentration, can be varied by the anesthesiologist. The larger the dose, the larger the area anesthetized (4). During use of hypobaric or hyperbaric solutions, position of the patient during injection and 5–10 min after injection is very important in achieving the desired anesthetic level (2). It is in this regard that the concept of "fixation" of local anesthetics in the subarachnoid space must be mentioned. Fixation refers to the time after intrathecal administration when changes in patient position no longer produce changes in the level of anesthesia (5,p119). Depending on the local anesthetic, the time for fixation ranges from 5 to 30 min (5,p119).

Barbotage, which is the technique of partial injection followed by aspiration of cerebrospinal fluid and then reinjection, was at one time believed to increase the spread of the local anesthetic by creating currents that carry the drug widely in the subarachnoid space

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Received from the Department of Anesthesiology, Stritch School of Medicine, Loyola University Medical Center, Maywood, Illinois. Accepted for publication November 26, 1985.

Address correspondence to Dr. Kleinman, Department of Anesthesiology, Loyola University Medical Center, 2160 South First Avenue, Maywood, IL 60153.

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(5,p108). However, more recent studies suggest that barbotage has no effect on the level of anesthesia (6,7). Nonetheless, barbotage was not used in this case.

The force and rate of injection were, at one time, also felt to affect the spread of anesthetic agent. This was felt to be secondary to the production of turbulence within the spinal fluid (2). Several studies now suggest that the force and rate of injection have no clinically significant effect on the spread of anesthetic agent in the cerebrospinal fluid (8,9).

The onset of action for subarachnoid lidocaine is almost immediate (10). Our case demonstrates that the level of anesthesia either continued to rise or suddenly ascended 40 min after injection into the subarachnoid space, despite our use of a reasonable dose (11). There are some mechanisms that perhaps can account for this. The injected lidocaine has a specific gravity of 1.035 and baricity of 1.027 at 37°C (10). Normal cerebrospinal fluid (CSF) has a specific gravity at 37°C of 1.0069 (2). Therefore, under normal conditions the solution of 5% lidocaine and 7.5% dextrose is very hyperbaric. Certainly if the CSF had a higher than normal baricity, then the distribution of the drug may have been affected. We did not measure the specific gravity of this patient's CSF. However, we feel that in the absence of neurologic disease, values of CSF specific gravity much beyond normal would be unlikely.

Since the injected lidocaine solution is very hyperbaric, a relatively long period of time may elapse before it becomes isobaric. During this time, the drug will tend to migrate to any dependent position in the subarachnoid space. Any motion in which the thorax becomes lower than the pelvis could cause cephalad spread of the anesthetic. We do not recall, however, any time in which this patient's thorax was lower than her pelvis. Another mechanism involves the concept of fixing of the drug to a nerve, which may be related to lipid solubility of the local anesthetic. We hypothesize that because lidocaine (partition coefficient 2.9) (12) is not as lipid soluble as other longer acting local anesthetics such as tetracaine (partition coefficient 4.1) (12) or bupivacaine (partition coefficient 27.5) (12), it will not fix as readily and therefore will be available for further cephalad migration in the subarachnoid space. In this regard it is important to point out that time of onset of a local anesthetic is related not only to its lipid solubility but also to its pKa (13). Therefore, it is possible for an agent such as lidocaine, with a relatively low pKa, to have a rapid onset time even though it is not as lipid soluble as tetracaine or bupivacaine.

This case, we believe, has an important clinical lesson. Reliance upon a single measurement of the sensory level of anesthesia 10 min after injection of a local anesthetic is neither safe nor reliable. Level of anesthesia should be tested repeatedly, both intraoperatively and postoperatively. In addition, when used for spinal anesthesia, lidocaine may have a tendency for delayed cephalad spread even 40 min after the administration of the local anesthetic. Level of anesthesia after subarachnoid block using hyperbaric lidocaine should be closely monitored to detect delayed cephalad spread.

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α-Pattern EEG during Pediatric Cardiac Operations under Isoflurane Anesthesia

P. D. James, MB, BS, FFARCS, G. A. Volgyesi, PEng, and F. A. Burrows, MD, FRCPC

Previous studies of the effects of isoflurane anesthesia on the electroencephalogram (EEG) in humans (1–3) have reported consistent findings of the appearance at sub-MAC concentrations of 12–14 Hertz low-amplitude activity superimposed on 2–6 Hertz high-amplitude waves. At about 1 MAC there is loss of amplitude in the 12–14 Hertz band leaving predominant 2–6 Hertz activity. From 1.5–2 MAC alternate low (6–8 Hertz) and high (2–6 Hertz) amplitude, activity appears in a burst-suppression pattern. We have studied six children who developed unusual EEG changes associated with the introduction of isoflurane during cardiac surgery. We present two typical cases in detail and discuss the implications for this group of patients. The six cases were part of a larger study looking at EEG changes in 48 children during cardiac surgery. Of the other 42 children in the study (all undergoing cardiac surgery), 22 received isoflurane, and none of these 22 children showed the unusual EEG changes associated with the introduction of isoflurane described here. The decision to use (or not to use) isoflurane in any of our patients was based solely on the clinical requirements of each patient (e.g., to aid rewarming, to control hypertension).

Case 1

A 4½-yr-old cyanotic child undergoing repair of tetralogy of Fallot was anesthetized with morphine sulphate (150 $\mu g \cdot kg^{-1} \cdot hr^{-1}$). During uneventful cardiopulmonary bypass (CPB) the patient was cooled to 21°C (esophageal). Isoflurane (1.5% inspired concentration) was introduced (Fig. 1b) and increased to 2 and 3% after 4 and 9 min to aid rewarming. The patient's EEG was monitored continuously with a Neurotrac compressed spectral array monitor (CSA), with F_3P_3, F_4P_4 electrode placings (international 10/20 system). The introduction of isoflurane was associated with an abrupt change in the dominant frequency of the EEG. The previously dominant δ/θ band (0.5–7.5 Hertz) was rapidly replaced by a high amplitude α (and low β) band (10–14 Hertz) with a reciprocal decrease in the power of the lower frequencies. At this point the esophageal temperature was 37.5°C, rectal temperature 29°C, Pa_{CO_2} 33 mm Hg, and Pa_{O_2} 228 mm Hg. During this period, mean arterial pressure (MAP) was 40 mm Hg (extracorporeal, nonpulsatile circulation) and did not decrease below this level. This dominant, rhythmic α-lowβ band persisted for approximately 18 min, at which point the isoflurane was turned off prior to coming off CPB. The α band abruptly disappeared (Fig. 1c), to be replaced by the previous δ/θ dominance. Figure 2 shows the development (and persistence) with time of the abnormal band and the reversion to a lower frequency dominance after the isoflurane was discontinued. This child suffered minor neurologic problems postoperatively (emotional flattening and seizure activity).

Case 2

A 10-yr-old boy with cyanotic heart disease was anesthetized with fentanyl (15 $\mu g \cdot kg^{-1} \cdot hr^{-1}$) and nitrous oxide (50%) in oxygen for creation of a Blalock–Taussig shunt. Premedication was with intramuscular pentobarbital (2 mg/kg), morphine sulphate (0.2 mg/kg), and atropine (0.02 mg/kg). Cardiopulmonary bypass was not used. Isoflurane was introduced 4¾ hr after induction of anesthesia with a view to discontinuing the fentanyl infusion to enable possible extubation at the end of the procedure. The EEG, monitored as in case 1, had been stable since the start of surgery, showing an EEG pattern characteristic of fentanyl anesthesia, consisting predominantly of lower frequencies (0.5–4 Hertz). When isoflurane (1.5% inspired concentration) was introduced (Fig. 3a) the

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Address correspondence to Dr. Burrows, Department of Anaesthesia, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8.

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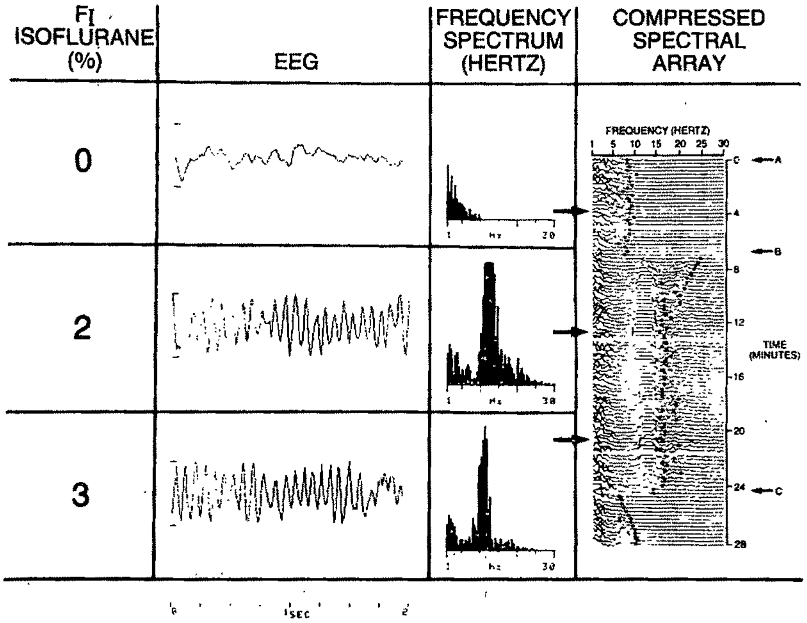

Figure 1. Electroencephalograph changes associated with isoflurane in case 1. Inspired (FI) isoflurane percentage is shown on the left. Isoflurane was introduced at (B) and discontinued at (C). Reciprocal decreases in the lower (0.5–7.5 Hz) frequencies can be seen.

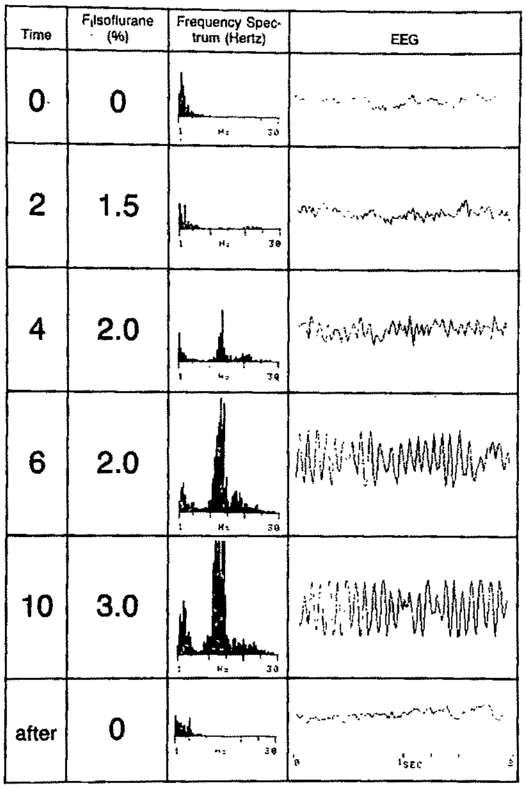

Figure 2. Development of changes in the EEG with time (minutes) after introduction of isoflurane in case 1. The return to previous δ/θ frequency dominance is seen 2 min after discontinuing the isoflurane. Inspired (FI) isoflurane concentration is shown.

dominant frequency of the EEG increased, with high amplitude activity in two frequency bands, α (8–11 Hertz) and low β (15–18 Hertz). The lower frequencies decreased in power. These bands persisted for 12 min with only a slight tendency to move to a lower frequency in the low β band. During this period, the lowest esophageal temperature was 35°C, the Pa_{CO_2} 43 mm Hg, and the Pa_{O_2} 63 mm Hg. Mean arterial pressure was at or above 80 mm Hg. With cessation of the isoflurane (Fig. 3b), the α and β bands rapidly disappeared, the EEG reverting to the previous low frequency pattern. Rechallenge with isoflurane 11 min later (Fig. 3c) produced the same change of patterns. The child made an uneventful postoperative recovery.

The details of all six children in whom we have found similar pattern changes are shown in Table 1. Table 1 also shows the frequency bands that developed in each case. None of the six children had known preoperative neurologic abnormalities. Only one child (case 1) suffered postoperative neurologic problems. The six children reported here were the only patients in our study group of 48 children to show these unusual EEG changes, although 22 out of the remaining 42 children in this larger study group received isoflurane during cardiac surgery.

Discussion

In contrast to previous reports documenting EEG changes with isoflurane, we have found unusual α (and low β) frequency bands of high amplitude and rhythmicity after the introduction of concentrations of isoflurane above 1 MAC in children undergoing cardiac surgery (1–3). The group of children studied so far is too small to make definitive analysis possible, but certain features are worthy of discussion.

We have been able to look for these changes only

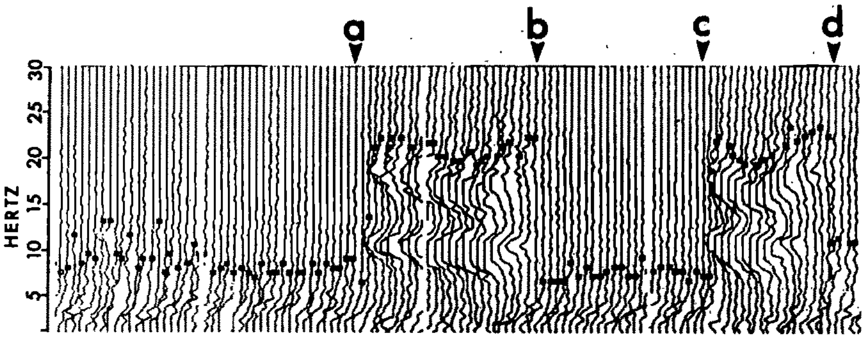

Figure 3. Compressed spectral array of unusual EEG changes with isoflurane in case 2. Isoflurane (1.5% inspired concentration) was introduced at (a) and (c), and discontinued at (b) and (d). Two high amplitude, rhythmic bands can be seen, 8–11 Hz and 15–18 Hz. The period (a–b) is approximately 12 min in duration.

in children undergoing cardiac surgery, so we cannot say if such changes are unique to this group of patients. As shown in Table 1, four of the six patients had cyanotic heart disease, a higher incidence than in our overall study group of 48 children (of whom 17 had cyanotic heart disease). The number of patients we have studied to date is too small to say whether the EEG changes we found represent a chance finding or whether a cause-and-effect association exists. All six children received a narcotic-relaxant anesthetic technique (as did the other 42 children) but varied widely in the degree of hypothermia utilized (Table 1). Changes in acid–base status or Pa_{CO_2} were unlikely to have caused the EEG changes we described because they were maintained within acceptable limits.

The changes in EEG we found associated with isoflurane do not show the EEG changes in frequency and amplitude during isoflurane anesthesia described by Eger and others (1–3). Instead, once a threshold concentration of isoflurane was attained (approximately 1.5% inspired concentration), the prominent α (and low β) band appeared (within 2–3 min) and maintained a high amplitude (peak amplitude approximately 400 μV) with remarkable rhythmicity until the isoflurane was discontinued. Only a slight decrease in frequency and amplitude was seen, even after 18 min of 1.5–3% isoflurane (inspired concentration) (Fig. 1). Although unable to measure end-tidal isoflurane levels, we can calculate (utilizing end-tidal studies recently performed on identical anesthetic systems) that alveolar isoflurane concentrations reached about 1.25% after 10 min of 1.5% inspired isoflurane. During anesthesia, utilizing 50% nitrous oxide and fentanyl (15 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ in case 2), this represents an alveolar isoflurane concentration of 1.5–2 MAC (4,5). EEG slowing would be expected with this concentration even over short periods of time. We have not seen burst-suppression patterns with isoflurane in these children, even with long periods of 2 MAC anesthesia. The tracings often show a reciprocal decrease in the lower frequencies on appearance of the α band (Figs. 1, 2, 3), a finding that contrasts sharply with other reports (1–3). Although we realize that a serious weakness in our study was our inability to accurately monitor isoflurane concentrations, we do not believe that any of the patients presented here were lightly anesthetized. Other workers utilizing comparable isoflurane concentrations have not reported similar findings (3). We have administered isoflurane to a group of 12 noncardiac patients (ASA I and II children, ages 5–9 yrs) and have not found any comparable anomalous EEG findings. We have, however, found, in line with reports of others, that at concentrations similar to those reported here the EEG showed a marked shift to the left with burst-suppression patterns at between 1.5 and 2 MAC isoflurane.

The changes in EEG we found in our six children were most commonly seen during rewarming or after coming off CPB. Whether this was due to the use of isoflurane to aid rewarming or to an effect of CPB in predisposing patients to this effect, we cannot say. Because two of the patients showed typical EEG pattern changes without CPB or significant hypothermia, the effect cannot be due simply to CPB or hypothermia.

Furthermore, the changes we observed in our children were unlike common patterns of seizure activity. The changes did, however, bear a strong similarity to the α-pattern coma (APC) reported after traumatic brain-stem infarctions, head injury, overdose with certain drugs (including phenobarbital), and cardiopulmonary arrest (6–8). Prognosis after APC depends on the etiology being better after drug overdoses than after cerebral hypoxia. Subtle neurologic deficits, however, cannot be ruled out in APC (6,8). In the clinical situations represented by the present study, we can rule out the normal α-rhythm and sleep spindles as a possible explanation of the changes we observed. The mechanism of APC has been postulated as brain-stem ischemia or depression interfering with the ascending reticulo-activating system (6,8). It appears that isoflurane may produce similar changes in the EEG as APC under different clinical circumstances. We can, however, only theorize over the

Table 1. Details of the Six Patients Observed Displaying Unusual EEG Changes during Cardiac Operations under Isoflurane Anesthesia

Number	Age (yr)	Cyanosis	Timing of effect	Mean arterial pressure (mm Hg)	Other agents	Esophageal temperature (°C)		Pa_{CO_2} (mm Hg)	Abnormal EEG frequency band (Hz)
						At time	Lowest		
1	4.5	yes	Rewarming	40[a]	Morphine	37.5	21.0	33	10–15
2	4	yes	After CPB	75	Fentanyl	37.0	22.5	41	8–14
3	5	—	After CPB	70–85	Morphine	37.5	13.0	37	10–14
4	10	yes	No CPB	80	Fentanyl/N_2O	35.0	35.0	43	8–11/15–18
5	10.5	—	No CPB	95	Morphine/N_2O	36.0	35.5	36	8–12
6	5	yes	Rewarming	50[a]	Morphine	35.2	26.0	35	8–11

Mean arterial pressure and Pa_{CO_2} measured at time of EEG change.
Abbreviation: CPB, cardiopulmonary bypass.
[a] Extracorporeal, nonpulsatile perfusion.

mechanism by which isoflurane, if it is the cause of the EEG changes we observed, might cause brain-stem ischemia (lowered regional perfusion pressure; direct toxic effect). However, the circulatory effects of CPB and hypothermia, especially in cyanotic children, may decrease the tolerance of the brain-stem to ischemic or toxic insults. No significant decrease in cerebral perfusion pressure occurred in any of our cases.

The cases we report leave many questions unanswered. The cause of EEG changes we have seen in children underoing cardiac surgery remains to be proven. Possible long-term neurologic effects associated with these EEG changes can be determined only by sophisticated postoperative neurologic evaluation, though to date we have no reason to believe these changes are not reversible. Similar EEG changes have also been reported in adults exposed to lower concentrations of isoflurane (9).

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Improved Remote Cardiorespiratory Monitoring during Radiation Therapy

Jyoti B. Pandya, MD, and John T. Martin, MD

Anesthesiologists are being asked more and more often to administer anesthesia to patients who are having high-energy radiation from a linear accelerator applied to a tumor site through an open surgical wound. Because of the nature of the radiologic equipment, intraoperative radiation therapy must be accomplished in the radiology suite and requires that only the patient be exposed to the active beam. Thus remote monitoring of a relaxed, mechanically ventilated subject with a carefully stabilized cardiovascular system is mandatory. These requirements provoke sufficient anxiety on the part of many anesthesiologists to cause them to avoid participation in such a procedure. We report here a simple refinement of cardiorespiratory monitoring in which the output of an esophageal stethoscope is converted to an electrical signal that is transmitted via a cable to a loudspeaker at the remote control point.

Materials, Methods, and Results

Our customary monitoring of an anesthetized patient undergoing intraoperative radiation therapy consists of a multilead ECG; an arterial catheter for blood pressure measurement and blood gas sampling; an oximeter, a respiratory pressure gauge, and an infrared carbon dioxide analyzer in the breathing circuit; and a temperature probe and stethoscope in the esophagus. A multilumen, flow-directed pulmonary artery catheter can be accommodated should the patient's condition require it. The usual intravenous lines for administration of warmed fluids and blood products completes a support and assessment capability identical to that available in the operating suite. On the wall of the protected control point, hard-wired to the patient (because of the shielded room), is an ECG/pressure monitor (Tektronix Model 414) identical to, and with its output slaved to, the unit on the anesthesia machine. Zoom-and-focus high-resolution television cameras aimed at the patient permit viewing of ventilation and can clearly display the dials and meters on the face of the anesthesia machine.

Although this arrangement permits useful and constant surveillance of the patient by the distant anesthesiologist, we have increased its safety by introducing a remote audio output for the esophageal stethoscope. Into the barrel of a 20-ml disposable plastic syringe we introduced an electret microphone (Radio Shack Cat #33-1058), the body of which had been expanded by enough adhesive wrappings to make a snug fit against the syringe interior. A 120-cm vinyl extension tubing (BD-8288) connects the syringe tip to the external end of the esophageal stethoscope; the syringe/microphone unit is mounted conveniently on the anesthesia machine. Two 7.7-m microphone extension cables (Radio Shack Cat #42-2379) were hooked in series, connected via an adaptor plug (Radio Shack Cat #274-325A) to the microphone cable, and led safely about the perimeter of the room to exit through an angulated conduit that emerges at the control point outside. The microphone extension cable was plugged into a portable speaker/amplifier (Radio Shack Cat #32-2028) chosen because of its intrinsic power supply and adjustable controls for tone and volume. The speaker was shelf-mounted next to the slave Tektronix unit (Fig. 1). Heart sounds and respiratory sounds can now be transmitted from the patient to the remote station during treatment.

At the end of a procedure, the microphone is removed from the syringe housing, and its battery is extracted to preserve its useful life. The remaining items of the apparatus are maintained intact for subsequent use. We have employed this equipment routinely for more than 2 yr without encountering problems.

Discussion

Conceptually, the technique of amplifying heart sounds and breath sounds that we describe is similar to that reported by Marsh et al. (1), although our equipment is different and we do not use several of their modifications. Skaredoff and Viguera (2) used a carbon

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Address correspondence to Dr. Pandya, Department of Anesthesiology, Medical College of Ohio, CS #10008, Toledo, OH 43699.

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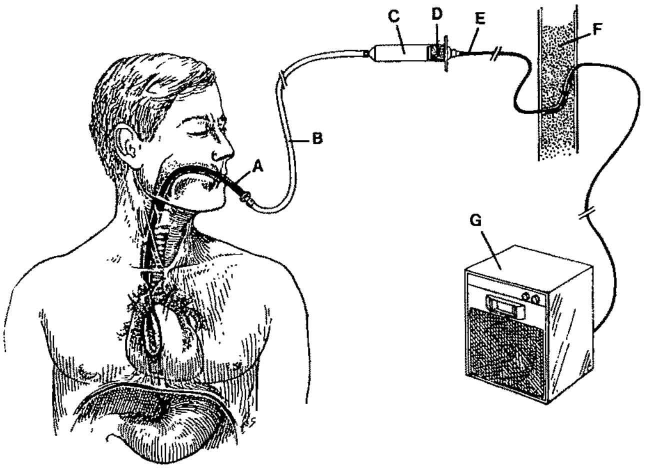

Figure 1. (A) Esophageal stethoscope; (B) 120-cm vinyl extension tubing; (C) the barrel of a 20-ml disposable plastic syinge; (D) electret microphone, (E) 7.7-m microphone extension cable; (F) Lead-reinforced concrete wall with angulated conduit; (G) speaker/amplifier unit at remote control point.

button microphone located paratracheally as a respiratory monitor; however, they made no mention of its ability to discern heart sounds.

Our purpose in developing this equipment system was to use readily available and compatible components that emphasize safety, simplicity, and economy. We also wished it to be reusable without the recurrent need for heat or chemical sterilization. Tonnesen et al. (3) have described an intraesophageal microphone for phonocardiographic recording; however, because our electronics are remote from the patient rather than intraesophageal, we believe that the hazard of microshock dysrhythmias in our system is almost nonexistent. The adjustability of tone and volume at the remote speaker makes sound recognition similar to that achieved through an ear piece. Any change in the sounds of mechanical ventilation, and particularly the sudden silence of an airway that has become disconnected from the respirator, is immediately evident at the remote speaker. This awareness exceeds that provided by watching respiratory motion on the video screen, although both modalities should be monitored. Similarly, cardiac dysrhythmias are audible, as well as visible on the ECG, and can be captured on the paper tracing of the slave ECG unit.

An added asset of our basic electronic system is that it retains the capability for daily routine use as an amplifier of sounds derived from a chest stethoscope placed in the suprasternal notch over the airway of a patient in whom anesthesia is being induced or maintained while a face mask is in use. Changes in respiratory sounds provoked either by airway obstruction or by weakened muscular effort can be readily recognized even by inexperienced observers.

The equipment described herein is easily available and durable. Its use improves remote monitoring for safe anesthesia of the patient undergoing intraoperative radiation therapy.

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Epidural Morphine Analgesia by Means of a Subcutaneously Tunneled Catheter in Patients with Gynecologic Cancer

Ottó Hamar, MD, S. Csömör Jr, MD, Z. Kazy, MD, and Z. Vigváry, MD

Analgetics and psychopharmaceuticals fail, even in high doses, to produce complete pain relief in patients with advanced gynecologic cancer. Due to their side effects, these agents, not totally effective, confine patients to bed and disturb contact with the environment and their families (1). To proceed with destructive neurosurgical methods to provide pain relief in patients with terminal cancer is pointless today (2), because epidural morphine analgesia (EMA) is capable of improving the quality of the patient's life in the last stage of cancer (3,4,5). Conventional methods of catheter fixation in patients requiring long-term management with epidural morphine, may, however, cause slight inconvenience to the patient when bathing, and the catheter can be displaced or damaged. To resolve these technical problems, we suggest subcutaneous tunneling of the epidural catheter (6).

Materials and Methods

Fifty women with advanced gynecologic cancer receiving epidural morphine analgesia were studied. In 25 cases (group A) subcutaneous tunneling was used and in 25 cases (group B) conventional methods were used, by which the catheter is not tunneled subcutaneously after insertion into the epidural space, but is fixed externally with clear adhesive tape to conduct the epidural catheter onto the abdominal wall.

Group A

Materials necessary in addition to those used to introduce a catheter into the peridural space include a scalpel, forceps, sutures, and a subcutaneous tunneling device (Portex Limited Hythe, Kent, England) that resembles a hollow knitting needle. The epidural catheter is introduced by a Tuohy needle into the epidural space, usually at level L3–4, and then guided 3–4 cm cranially according to standard procedures. We administer a short-acting local anesthetic (10 ml 1% lidocaine) through the catheter after it is in place to ensure pain relief for the subsequent tunneling of the catheter subcutaneously. (We prefer this method to local infiltration of the operative site.) An incision is then made extending cranially and caudally 0.1–1.0 cm from the point of insertion of the Tuohy needle; the needle is then removed. The skin is then lifted with forceps, and the tunneling device is introduced subcutaneously and guided laterally. At the posterior axillary line a second incision is made near the tip of the tunneling device. When the tunneling device appears through the second incision, the catheter is threaded into the device, after which the tunneling device is removed laterally through the second incision. By repeating the procedure one or two times, the catheter can be advanced to a position on the anterior abdominal wall. We usually have the distal end of the catheter exit from the skin in the midclavicular line at the lower edge of the rib cage. The wounds at each incision site are closed with one suture each. The catheter can be cut to the desired length. A bacterial filter (disc or flat type) is then attached to the catheter, after which the catheter is secured with opsite or adhesive tape.

Group B

Epidural morphine analgesia was carried out on 25 patients using the conventional technique, whereby the catheter was placed in the desired position and secured to the skin with clear adhesive tape. Each patient was taught to self-administer morphine solution as prescribed and was monitored by out-patient visits at intervals of 7–10 days. The average single dose was 8 mg (2–20 mg) and the total daily dose averaged 14 mg (4–26 mg). Pain relief lasted up to 12 hr with each injection even over a period of days. We found no signs that tolerance had developed.

Results

Pain relief was complete in each patient in both groups. The average period of treatment with EMA was 69

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Address correspondence to Dr. Hamar, H-1082 Budapest, Üllői u.78/a, Hungary.

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days (2–289 days) in group A and 65 days (1–201 days) in group B.

Complications

In group A, 24 patients were complication free during their course of treatment. One catheter became plugged and had to be removed. In group B, 20 patients were complication free. Two catheters became obstructed, and two catheters slipped out of the epidural space. In one patient local infection developed at the site of insertion of the Tuohy needle.

Discussion

The disc type filter is not ideal for fixation against the skin and can cause the catheter to kink if not properly splinted. The flat filter lies flat against the patient's skin, ensuring both comfort and full flow through the catheter. EMA is effective for the relief of terminal pain caused by gynecologic cancer. Subcutaneous tunneling of the catheter causes fewer complications. It is easier to manage and less inconvenient to the patients than are catheters that exit from the posterior or dorsal site of insertion of the catheter into the epidural space.

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Ventricular Tachycardia and Hypotension with Amniotic Fluid Embolism during Cesarean Section

Kamlesh Shah, MD, Roberta Karlman, MD, and John Heller, MD

Obstetrical patients presenting with acute or chronic hypertension usually do not develop myocardial ischemia or arrhythmias during cesarean section. We report a case of life-threatening ventricular tachycardia in a hypertensive patient secondary to documented amniotic fluid embolism during cesarean section under lumbar epidural analgesia.

Case Report

A 41-yr-old woman, para 1, gravida 2, at 38½ weeks gestation was scheduled for urgent repeat cesarean section because of failure of labor to progress. She was 162 cm tall and weighed 85 kg. She had gained 18 kg during the current gestation. Her medical history revealed a previous pregnancy 10 yr ago associated with preeclampsia for which she had undergone cesarean section. The chronic hypertension that persisted after the delivery was treated with methyldopa, 250 mg four times per day. Prior to the current gestation, the patient complained of dyspnea on moderate exertion and left-sided chest pain, symptoms she continued to have during the current gestation. The patient's complaint of chest pain was mostly related to moderate exertion, lasting 1–5 min, and was relieved by rest. She took no medications for the chest pain. Six weeks prior to this cesarean section, the patient was examined by a cardiologist. An echocardiogram and electrocardiogram showed left ventricular hypertrophy but no evidence of myocardial ischemia. The cardiologist decided not to subject the patient to more definitive diagnostic tests such as treadmill exercise or coronary angiography during her pregnancy.

The cesarean section was planned under lumbar epidural analgesia. Monitoring prior to anesthetic induction included ECG, intraarterial blood pressure, pulmonary artery and pulmonary capillary wedge pressure, and skin temperature. Hemodynamic findings immediately prior to epidural analgesia included heart rate (HR) 80 beats/min, arterial blood pressure, 220/100–280/120 mm Hg, pulmonary artery pressure (PAP), 33/8 mm Hg, and mean pulmonary capillary wedge pressure (PCWP), 14 mm Hg. Lead II and chest lead V_5 ECG tracings showed no evidence of myocardial ischemia or dysrhythmias.

The patient received 600 ml of lactated Ringer's solution with 5% dextrose before initiation of epidural analgesia. The lumbar epidural space was identified and, after an appropriate test dose of 3 ml, a total of 25 ml of 0.5% bupivacaine was injected through a 17-gauge Tuohy needle over a period of 10 min. A 20-gauge epidural catheter was threaded into the epidural space. The operation started after a sensory level of T_6 was achieved. The patient remained hemodynamically stable during this period with an arterial pressure of 190/100 mm Hg and a PCWP of 9 mm Hg.

Immediately prior to the delivery of the fetus, the patient complained of pain below the left breast during uterine manipulation. Heartrate and systemic blood pressure did not change significantly, but the PAP increased from 35/9 to 38/16 mm Hg. There was no indication of ischemia on ECG, in lead II or in chest lead V_5. Eight minutes after the skin incision, a male infant was delivered with Apgar scores of 8 and 9 at 1 and 5 min. The patient continued to complain of left-sided chest pain during the delivery of the fetus and placenta.

A diagnosis of myocardial ischemia was entertained because of the chest pain and increased pulmonary artery diastolic pressure. An infusion of intravenous nitroglycerin 0.1 mg/ml was initiated at a rate of 30 ml/hr without relief of chest pain. Ten minutes after the initiation of nitroglycerin therapy, three episodes of ventricular tachycardia with a rate ranging from 160–190 beats/min were observed over a period of 2 min. Each episode lasted about 8–10 sec and was associated with a decrease in systolic arterial pressure

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Received from the Department of Anesthesiology, Stritch School of Medicine, Loyola University of Chicago, Maywood, Illinois. Accepted for publication December 17, 1985.

Address correspondence to Dr. Shah, Department of Anesthesiology, Loyola University Medical Center, 2160 South First Avenue, Maywood, IL 60153.

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to 70 mm Hg. Intravenous lidocaine, 50 mg, administered twice converted the ECG to sinus rhythm. However, after 2 min of normal sinus rhythm, episodes of ventricular tachycardia with a rate of 170 beats/min recurred, associated with a decrease in systolic arterial pressure to 70 mm Hg. It was decided to perform an orotracheal intubation to protect the airway and achieve adequate oxygenation. Intubation was accomplished uneventfully. General anesthesia was induced to avoid probable awareness or recall of the events and was maintained with 12.5 mg of intravenous diazepam and total 150 mg of ketamine administered over a period of 45 min. Metocurine was administered to facilitate controlled ventilation with 100% oxygen. The patient's hemodynamic state did not change significantly during the remaining intraoperative and postoperative period. Intravenous nitroglycerin infusion, 0.1 mg/ml, was continued at a rate of 30 ml/hr to maintain PCWP in the range of 8–12 mm Hg. The patient was extubated 2 hr later in the recovery room.

A mixed venous blood sample from the distal lumen of the pulmonary artery catheter was sent to the laboratory for microscopic examination. Electrocardiogram and plasma levels of cardiac enzymes were normal in the immediate postoperative period and remained normal for the next 3 days. A diagnosis of amniotic fluid embolism was confirmed by the presence of fetal cells, debris, and lanugo hair in the mixed venous blood sample. The patient's vital signs remained stable, and she was asymptomatic during the remainder of her hospital stay. She was discharged on the seventh postoperative day without residual complications.

Discussion

Amniotic fluid embolism is an unpredictable, largely unpreventable, and mostly untreatable catastrophe. The reported incidence of amniotic fluid embolism ranges from 1 in 8000 to 1 in 80,000 births. In his review of 272 cases of amniotic fluid embolism, Morgan found a mortality rate of 86% (1).

Amniotic fluid embolism most commonly occurs during labor or delivery. It is postulated to occur after a tear or a defect in the membranes adjacent to open maternal vessels either at the placental implantation site or at the lower uterine segment. Other possible conditions associated with amniotic fluid embolism include traumatic disruption of the uterus, cesarean section, placenta accreta, amniotomy, and insertion of intrauterine pressure monitoring catheters.

Clinical features of amniotic fluid embolism in the peripartum period include dyspnea, tachypnea, cyanosis, and, rarely, chest pain (2). These patients may present with hypotension out of proportion to blood loss. Cardiorespiratory collapse with hypotension and supraventricular or ventricular arrhythmias, bradycardia, and asystole are not uncommon. Pulmonary hypertension is almost invariably noticed and may be the initiating event for cardiorespiratory collapse (3). Other features of amniotic fluid embolism include pulmonary edema, acute left ventricular failure, hypotension, unconsciousness, aspiration of stomach contents, disseminated intravascular coagulopathy, bronchospasm, and seizures. Definitive diagnosis is established by demonstrating fetal squamae, mucin, meconium, or lanugo hairs in mixed venous blood or in the small vessels of the lungs at autopsy (1,4,5).

This patient had a history of chronic hypertension with chest pain on moderate exertion. The ECG and echocardiogram demonstrated left ventricular hypertrophy. This history and preoperative ECG and echocardiographic findings led us to make an empirical diagnosis of myocardial ischemia as the precipitating cause of ventricular tachycardia. Though there were no ECG signs of myocardial ischemia in either the intra- or postoperative period, myocardial ischemia at the time of occurrence of ventricular tachycardia could not be ruled out because these episodes were associated with a significant increase in the pulmonary artery diastolic pressure. Amniotic fluid embolism during the intraoperative period might have contributed to the chest pain, which is a rare presenting symptom of amniotic fluid embolism. The ventricular tachycardia and decreased myocardial compliance as evidenced by increased pulmonary artery diastolic pressure that occurred in this patient could have been from amniotic fluid embolism with or without myocardial ischemia.

Pulmonary hypertension secondary to amniotic fluid embolism is associated with right ventricular failure. The use of intravenous nitroglycerin shortly after the patient's complaint of chest pain might have prevented the occurrence of severe pulmonary hypertension and its sequelae: right ventricular failure, pulmonary edema, shock, and coagulopathy. A pulmonary artery catheter was placed in this patient prior to induction of epidural analgesia to treat complications that the patient might develop from suspected coronary artery disease. This monitoring device helped us both in treating amniotic fluid embolism and in confirming the diagnosis. Without the pulmonary artery catheter in place, it would not have been possible to obtain a true mixed venous blood sample. Although right atrial blood sampling may show fetal cells, mucin, or lanugo hairs, mixed venous blood sample from a pulmonary artery catheter is more reliable in establishing a definitive diagnosis of amniotic fluid embolism.

Schaerf et al. (6) reported a similar case of amniotic fluid embolism in which early use of a pulmonary artery catheter helped in establishing the diagnosis and successful hemodynamic management of the patient. However, the pulmonary artery catheter was placed in that patient after the occurrence of amniotic fluid embolism. Though the placement of the catheter helped in the management of the pulmonary hypertension, early diagnosis of pulmonary hypertension could not be made. In our patient, presence of the pulmonary artery catheter helped us in the immediate detection of increase in the pulmonary artery diastolic pressure. Initiation of nitroglycerin therapy and normalization of the pulmonary artery diastolic pressure did not lead to immediate right or left heart failures as in the patient of Schaerf et al.

In concluding this case report, we suggest that in suspected cases of amniotic fluid embolism, immediate placement of a pulmonary artery catheter, if not already in place, and vasodilator therapy might prevent the catastrophic sequelae of pulmonary hypertension secondary to amniotic fluid embolism. The pulmonary artery catheter will also help establish a definitive diagnosis of amniotic fluid embolism.

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Normeperidine Toxicity

Peter J. Armstrong, MB, BS, FFARACS, and Andrew Bersten, MB, BS, FFARACS

Meperidine hydrochloride is the most commonly prescribed opioid analgesic for postoperative pain in our hospital. Biotransformation of meperidine may lead to a potentially toxic metabolite, normeperidine. We describe two cases of apparent normeperidine toxicity and discuss reasons for normeperidine accumulation.

Case 1

A 40-yr-old woman with disseminated carcinoma of the colon was admitted with a subacute intestinal obstruction. This was treated conservatively for 5 days before palliative bypass surgery was performed. She had been seen by the Pain Management Unit over the previous 4 months in an attempt to control severe upper abdominal pain thought to be related to documented intraabdominal metastases. Three months before admission, an implantable portal system (1) was inserted for the long-term epidural administration of opioids starting with two daily doses of morphine sulphate, 10 mg, in 10 ml normal saline. This provided effective pain control up to the time of the present admission.

The findings at laparotomy were of a large tumor mass occupying most of the right iliac fossa and pelvis, widespread peritoneal seeding, and a tumor involving the anterior abdominal wall. The mass was bypassed and the bowel decompressed. Her postoperative epidural morphine doses were increased to 30 mg every 6 hr, but she remained in pain. An intravenous infusion of meperidine was added and its rate increased progressively as the pain remained refractory. Twenty-four hours postoperatively she had a grand mal convulsion of 5 min duration. No prodromal symptoms or signs were noted. The convulsion was managed by maintenance of her airway, supplemental oxygen by mask, and intravenous diazepam, 5 mg. She had received 2800 mg meperidine by that time. A blood sample was taken 30 min after the grand mal convulsion from the antecubital fossa on the side opposite to her intravenous infusion. The whole blood concentrations of meperidine and normeperidine were 2.9 μg/ml and 4.3 μg/ml, respectively.

No evidence of central nervous system malignancy was found; serum electrolyte, glucose, and calcium levels were normal, as were arterial blood gas tensions. There was no significant past history. There have been no further convulsions or neurologic sequelae. Subsequent pain relief was provided effectively with epidural morphine.

Case 2

A 38-yr-old woman developed numerous problems following surgery for morbid obesity. After unsuccessful gastric surgery, she had a jejuno-ileal bypass that subsequently required revision because of metabolic problems. Two weeks after this second operation, further surgery was required to release a small bowel obstruction during which a gastrostomy was performed. For the next two weeks she received, on average, 1000 mg per day of meperidine by intermittent intramuscular injection. During this time she became increasingly agitated, complained of worsening pain, and was noted to have frequent myoclonic jerks. In the absence of other causes, a provisional diagnosis of normeperidine toxicity was made. Intramuscular morphine was substituted for meperidine, and subsequently normeperidine and meperidine blood concentrations were measured at the times indicated (Table 1). Clinically she improved and went home on day leave 3 days after the meperidine was discontinued. Serum electrolyte, calcium, phosphate, and magnesium levels were normal at the time of diagnosis of normeperidine toxicity, as were liver and renal function tests.

Discussion

Meperidine, first described in 1939, is today a widely used opioid analgesic. Normeperidine toxicity was

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Address correspondence to Dr. Armstrong, Department of Anaesthesia and Intensive Care, Flinders Medical Centre, Bedford Park, S.A. 5042, Australia.

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Table 1. Data on Case 2

	Meperidine μg/ml	Normeperidine μg/ml
Hours after last dose		
1	0.692	1.562
31	0.050	0.389
124	0.021	0.077
Elimination $T_{1/2}$	7.5 hr	35 hr

Blood samples were taken from the antecubital fossae. Intravenous therapy was infused via a central catheter.

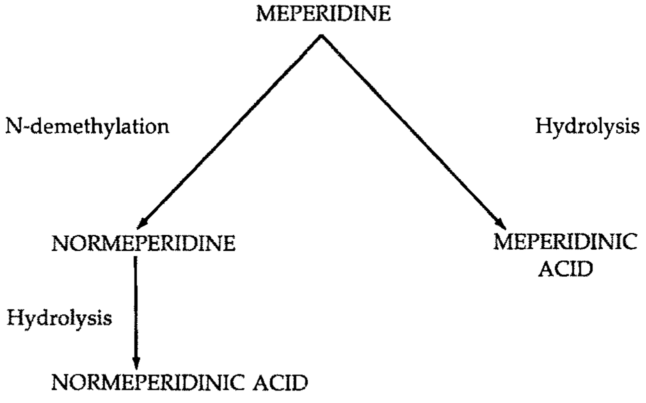

Figure 1. Major biotransformation pathways of meperidine in man. Adapted from Mather and Gourlay (6).

first described in primates in 1961 (2) and subsequently in humans in 1977 (3).

Meperidine is normally eliminated by two hepatic metabolic routes, hydrolysis to meperidinic acid and N-demethylation to normeperidine (Fig. 1). Normeperidine is then hydrolyzed to normeperidinic acid (4). Excretion of normeperidine and normeperidinic acid is primarily renal. The acid metabolites are pharmacologically inert, but normeperidine has appreciable pharmacologic activity. Typical values of the elimination half-lives of meperidine and normeperidine are 3–6 hr and 15–40 hr, respectively. Therefore, prolonged administration of meperidine may lead to an accumulation of normeperidine, especially in the presence of renal impairment.

To date, toxic effects of normeperidine in humans have not been studied directly by administration of this metabolite. However, there is circumstantial evidence in humans and direct evidence in animals that normeperidine may cause central nervous system excitability (5,6). Kaiko et al. (5) have described a progression of signs of central nervous system excitation such as tremors, myoclonus, and grand mal convulsions that correlate more with plasma normeperidine concentrations than with plasma meperidine concentrations. In both patients reported here, whole blood meperidine concentrations were well within the range previously reported as providing significant pain relief (6). Comparatively less alternative opioid (morphine) was required subsequently for pain relief. Therefore it is possible that symptoms interpreted as pain or discomfort, e.g., tremor, restlessness, and myoclonus, may have been due to normeperidine toxicity. Whole blood normeperidine concentrations in both patients were comparable to the highest concentrations reported by Kaiko et al. (5). The mean normeperidine plasma concentration associated with myoclonus and grand mal convulsions reported by Kaiko et al. (5) was 0.81 μg/ml. We believe it is valid to compare whole blood meperidine and normeperidine levels, as measured in this report, to other studies measuring plasma meperidine and normeperidine because the blood/plasma ratio of meperidine is close to unity (7).

If normeperidine toxicity is suspected, meperidine administration should be ceased. Grand mal convulsions should be treated as required in each case. In patients with high concentrations of meperidine and normeperidine it is possible that meperidine may mask the excitatory effects of normeperidine. Naloxone does not reverse normeperidine toxicity (5). It may, in fact, exacerbate the condition by antagonizing the depressant effect of meperidine. Normal neurologic function may not return for some days after cessation of meperidine because of the long elimination half-life of normeperidine.

In conclusion, this form of central nervous system excitability associated with normeperidine toxicity, though not frequently recognised, deserves consideration in patients receiving large doses of meperidine. Normeperidine toxicity may be prevented by avoiding prolonged administration of meperidine, especially to patients with impaired renal function. In circumstances where prolonged administration of an opioid agonist is anticipated, a drug without an active metabolite, e.g., morphine, would be a wiser choice.

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Letters to the Editor

Resistance to Pancuronium

To the Editor:

The fascinating report by Callanan (1) on profound relaxant resistance in an ICU patient provokes the following commentary concerning mechanism and a pseudosteady state situation while measuring dose response characteristics.

Concerning mechanism: a) During the nine days she was confined to bed, this young woman undoubtedly developed some degree of total body disuse atrophy, a disorder associated with relaxant resistance (2,3). b) Most likely, she developed, at least in part, a denervation-type lower motor neuron lesion secondary to the week-long intermittent paralysis, although the intact motor nerves would still have provided tropic effects (4). This would result in receptor spread and relaxant resistance (3). c) Her multiple drug regimen included diphenylhydantoin—it, and perhaps other of her medications, are associated with pharmacodynamic alterations resulting in relaxant resistance (5), as well as enzyme induction and possibly more rapid clearance.

Concerning dose–response characteristics: the repeated administration for a week of a slowly cleared drug such as pancuronium probably resulted in a virtual equilibrium across the various tissues of the body, as opposed to the nonequilibrium of a single dose or brief administration. Under these circumstances, the pseudosteady state is associated with increased relaxant resistance, even though the lesion is identical. We noted this difference in apparent dose–response in dogs with equivalent degrees of immobilization disuse atrophy—2- to 3-fold relaxant resistance in a nonequilibrium situation (2), and 10-fold resistance in a pseudosteady state situation (3). Most clinical reports of relaxant resistance involve an acute equilibrium situation, and therefore have noted less marked resistance.

Gerald A. Gronert, MD
Department of Anesthesiology
Mayo Medical School
Rochester, MN 55905

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Controlled Drug Accountability

To the Editor:

The recent article by Moleski et al. considers a system of individualized anesthesia boxes for controlled substance accountability in the operating room "unacceptable" (1). Theoretical reasons stated in the article for this negative conclusion include a "larger and expensive working inventory of drugs" and anesthesia personnel not wishing to be personally responsible for large quantities of controlled drugs. In theory, the system may be unacceptable. In actual practice, it works very well.

At my hospital, to improve accountability in an efficient and economical manner, I have removed all controlled drugs from the operating room and placed them back in the pharmacy. Each morning, each anesthetist signs out his or her own "Controlled Drug Box" (containing basic narcotics, thiopental, and diazepam) from the pharmacy, administers anesthetics from it, and returns it to and reconciles it with the pharmacy at day's end. No anesthetist or operating room personnel have access to the central supply of controlled drugs. No additional pharmacist is needed. Initial cost of small metal tool boxes (32 x 17 x 13 cm) and padlocks is minimal (about $10–15 for each unit). A larger inventory of drugs is not necessary, and anesthetists do not carry "large quantities of controlled substances." Significant errors in controlled drug accountability have been eliminated.

This system of individualized anesthesia boxes is simple, inexpensive, requires minimal equipment, and no additional personnel. Accountability is individualized, access is limited, and a quality assurance audit trail is established by entering patient drug utilization on the pharmacy's computer (as is done for all drug utilization in the hospital).

The objectives of any such drug control system are to improve accountability and decrease the incidence of drug abuse by limiting access to controlled drugs and establishing an accurate audit mechanism. The articles by Moleski et al. (1) and Adler et al. (2) describe systems that fulfill the objectives, but they are systems that may be unnecessarily complicated and expensive. The system we use is inexpensive, simple, effective, and efficient. Detailed information (forms, etc.) will be provided by the author on request.

Edson O. Parker, MD
Chief, Anesthesiology
Eisenhower Army Medical Center
Fort Gordon, GA 30905-5650

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In Response:

We thank Dr. Parker for his comments concerning controlled drug accountability. Certainly the location of dispensing controlled substances is important. In our operating suite, which has a large number of anesthesiologists working simultaneously, the use of a satellite pharmacy is more cost effective. In addition, if the pharmacy is at some distance from the operating room, it may be difficult for personnel to go to the pharmacy, retrieve their drugs, and then return to the operating room. The availability of these drugs on an emergency basis may also be hampered. However, in hospitals where the pharmacy is much closer to the operating room and there is not a large demand early in the morning, a system such as Dr. Parker suggests is obviously workable.

We would like to reemphasize that drug dispensing is only one part of this controlled substance accountability system. We feel the more crucial parts of the system are the audit trail, which documents the record keeping of administration of the drugs, and the chemical auditing of syringes (on a random basis) that are returned to the pharmacy.

Ronald Moleski, PhD
Department of Pharmacy
Yale New Haven Hospital

Paul G. Barash, MD
Department of Anesthesiology
Yale University School of Medicine
New Haven, CT 06510

Failure of Aminophylline to Antagonize Midazolam Sedation

To the Editor:

I read with interest the report of the use of aminophylline to reverse oversedation with benzodiazepines (1). I have, in the last 18 months, used aminophylline on six occasions in attempt to awaken oversedated patients, but with a much lower success rate. Two patients had been receiving sedation for carotid angiography, one patient for lumbar sympathetic blockade, and three for hip surgery under spinal anesthesia. They were all unpremedicated except for one, who had received 20 mg temazepam 2 hr previously. They were given between 2.5 and 7.5 mg midazolam intravenously at the start of the procedure, as considered clinically appropriate. In addition, the patients for carotid angiography had received 15 mg pentazocine intravenously at the same time. The procedures lasted between ½ and 2 hr. The patients were considered oversedated if, at the end of the procedure, they did not respond to verbal command. All the patients were given 75 mg aminophylline slowly intravenously and observed. (This dose was repeated in one case after 15 min). No change in the level of consciousness was noted in five of the patients, until they woke up, apparently spontaneously, between ½ and 1½ hr later. There was no other cause for their prolonged somnolence. Only in one patient (one of these undergoing hip surgery) was the dramatic awakening as reported by other authors seen (1,2).

It is impossible to compare results with such small groups under such uncontrolled conditions. However two possible explanations may be considered. First, the drug used (midazolam) is different from other benzodiazepines pharmacokinetically and pharmacodynamically. Second, it may be that there is wide individual variation within the population in regard to the adenosine amplification of the γ-amino butyric acid system (2). This hypothesis is currently being investigated.

J.W. Sleigh, FFARCS
Department of Anaesthetics
Godfrey Huggins School of Medicine
University of Zimbabwe
Avondale
Harare, Zimbabwe

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Static and Dynamic Considerations in Gastric Barotrauma

To the Editor:

Barker and Karagianes (1) may have made an improper assumption as a basis for their mathematical proof for determining the cause of lesser curvature rupture in gastric barotrauma. The law of Laplace allows recognition of the relationships of the effects of pressures internal to a spherical/cylindrical elastic body or membrane and the tension exerted by this pressure on the membrane, $P = T(1/R + 1/R')$, in a static system at equilibrium. If the pressure (P) is positive, the radii (R) and tension (T) are also positive and proportional in this truly elastic membrane situation. By assigning negative signs to the radius when located outside the pressure area with truly compliant elastic membranes, one finds that tension develops when P and R are of the same sign (Fig. 1). $-P$ and $-R$ in Figure 1*B* are contrived, as the pressure outside of the chamber in reality causes the hemispherical membrane to "flop" into the chamber, and positive tension develops proportional to the positive pressure and positive radius as now viewed from outside the chamber (Fig. 1C). In using the above equation one assumes that only forces resulting from the effect of the internal pressure are in effect and that all portions of the membrane are equal in thickness and elastic characteristics. This results in a situation where negative pressure, tensions and radii do not occur singly.

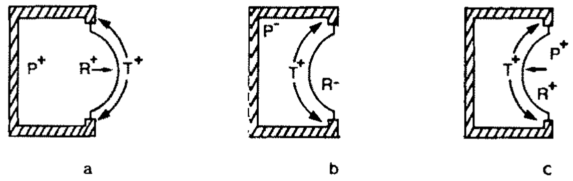

Figure 1. Relationships in effect as a result of pressures exerted upon an ideal elastic membrane with respect to Laplace's law. Plus and minus signs denote the valence of factors P, R, and T in the development of wall tension. In B and C, the valences of pressure (P) and radius (R) are of the same sign in each case, resulting in positive wall tension (T), and the difference is contrived by considering P internal or external to the box.

Laplace's law may be utilized to help explain gastric barotrauma though, if one recognizes the nonhomogenicity of the stomach wall and introduces the effects of wall thickness (h) into the equation for a spherical body: $P = T(2h/R)$. The lesser curvature commonly exhibits large longitudinal folds along its length, the plicae longitudinales mucosae, allowing considerable variations in the wall thickness to occur. The thinner portions of the wall thus become more susceptible to the relatively increased wall tensions here. This may also help to explain the longitudinal lesions observed in gastric barotrauma.

The matter is more fully appreciated when other dynamic factors are considered. The entrance of air into the stomach occurs most likely in a fashion that produces oscillations within the gas volume contained, as well as wave fronts that travel along the tissues encountered below the gastro-esopageal (G-E) junction. These low frequency sound or shock waves are commonly created by the G-E junction "flapping in the breeze" like vocal cords and would be expected to be directed primarily toward the lesser and inferior greater curvature tissues. This could additionally stress the thinner walled portions of the lesser curvature in a state of tension and promote tearing. Functionally the lesser curvature is also less involved in expanding to contain large ingested volumes and is perhaps at an increased liability of incurring lesions secondary to a relatively reduced state of dynamic compliance, partial thickness or wholly, even before the end filling volume of the stomach is reached. Finally, a partial tear would enhance the likelihood of further damage through subsequent insult at this site and any mucosal tear would set the stage for ongoing digestive injury that may only be fully appreciated at a later time. In respect to autodigestion, lesser curvature tissues have long been noted to be a prominent focus minori resistenciae (point of least resistance) in gastric peptic ulcer disease.

Paul M. Kempen, MD
Department of Anesthesiology
University of Michigan Hospitals
Ann Arbor, MI 48109-0010

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Postoperative Sagittal Sinus Thrombosis after Spinal Anesthesia

To the Editor:

In addition to the relatively frequent complications of postlumbar headache, a variety of more seldom and more serious complications to spinal anesthesia have been described (1,2,3). The occurrence of intracranial sinus thrombosis has not been previously reported in connection with spinal anesthesia. We recently encountered such a case, however, that of a 35-yr old man, otherwise completely healthy, scheduled for a hemorrhoidectomy.

The patient had been premedicated with 25 g promethazine, 0.5 mg atropine, both intramuscularly, and 5000 IU heparin subcutaneously. He arrived at the operating room in a very anxious state, however; and, after venous cannulation, his blood pressure decreased from 130/90 to 90/55 mm Hg. Despite this, 80 mg of a hyperbaric 4% solution of mepivacaine was injected with the patient in the sitting position, through a 25-gauge needle in the midlumbar subarachnoic space. This was followed by a further drop in the blood pressure to 80/60 mm Hg. The patient was immediately placed in the supine position, 0.5 mg dihydroergotamine was injected intravenously, and 500 ml of 6% dextran 70 were given. Within 15 min the pressure was 120/80 mm Hg, and it remained above this value throughout the operation, which was performed with the patient in the lithotomy position under satisfactory spinal anesthesia. No sedative or other drugs were given intraoperatively.

Postoperative heparin, 5000 IU subcutaneously, was started three times per day (routinely given for six days). On the first postoperative day, however, the patient complained of severe postural headache. Treatment consisted of intravenous hydration and analgetics. No epidural blood patch was attempted, and the headache persisted at least until the night between the fourth and fifth postoperative day, when the patient complained of paresthesias and decreased muscular force in the left arm. Approximately 6 hr later the left arm was paralyzed, and within another 2 hr complete left hemiparesis was present, including a facial nerve palsy. The patient was transferred by helicopter to a specialized neurologic center. There further progession occurred in the form of focal and generalized convulsions and somnolence. Cranial computed tomography, EEG, and diagnostic lumbar puncture yielded only nonspecific changes. An angiography showed complete thrombosis of the superior sagittal sinus.

After establishment of this diagnosis, anticoagulation therapy was initiated with fenprokumon. Within 2 weeks the symptoms completely disappeared, and the patient was discharged with continued anticoagulation therapy for 6 months.

This rare complication in a young, healthy patient remains obscure. Perhaps it was a complication of the spinal anesthesia itself, e.g., a chemical arachnoiditis; a result of changes in intracranial blood flow due to the hypotension; or a consequence of changes in intracranial pressure that also resulted in the postoperative postural headache. Or, the complication may not have been directly related to spinal anesthesia. The fact that onset of severe postural headache and onset of neurologic symptoms were so closely related suggests, however, that the two may have been related. It is also interesting that prophylaxis with low-dose heparin was ineffective in preventing thrombosis of the sagittal sinus.

John Schou, MD
Michael Scherb, MD
Department of Anesthesia
Städt. Krankenhaus
D-7850 Lörrach
Federal Republic of Germany

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Difficult Removal of Epidural Catheters in the Sitting Position

To the Editor:

We recently encountered difficulty in removing epidural catheters from two women in whom epidural analgesia was established for pain relief during labor. In each case, a 16-gauge Tuohy needle was inserted in the third lumbar intervertebral space with the patient in the sitting position. The epidural space was identified by the loss of resistance to air. Portex epidural catheters were inserted without difficulty in both patients. In one patient the catheter was directed cephalad, and in the other caudad. After removal of the needle, each catheter was secured with its tip 12 cm from the point of entry into the skin. Satisfactory analgesia was produced in both cases.

After delivery in each case, attempts were made to remove the catheter with the patient seated. Gentle traction on the catheters met with firm resistance on numerous attempts, in spite of various positional changes while in the sitting position. Both patients were subsequently placed on their sides in a modestly flexed position. The catheters were then removed without difficulty. The catheters were checked on removal and in each case found to be intact, with no kinks, looping, knots, or nicking.

A search of the literature revealed several reports of difficulty removing an epidural catheter. The vertebral arches (1), lumbar fascia, vertebral processes (2), ligamentum flavum (3), posterior vertebral joints (4), and the lumbar 2–3 nerve roots (5) have all been implicated as sites where the catheter may be gripped on withdrawal.

In our cases the catheters were not damaged; thus it is difficult to implicate any particular structure in preventing withdrawal of the catheters in the sitting position. The catheters may have been held by planes of ligaments and/or soft tissues that were altered when the patients' positions were changed.

The above cases suggest that if removal of epidural catheters in the sitting position is difficult, the patient should be placed in the lateral flexed position.

Patrick Rice, MB
C.T. Ethans, MD
Department of Anesthesia
University of Manitoba
Health Sciences Centre
Winnipeg, Manitoba
Canada R3E 0W3

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Transillumination of the Trachea with a Lighted Stylet

To the Editor:

We have used the Flexilum™ surgical light (Concept Corporation, Clearwater, FL) as a lighted stylet for a number of years in instances in which tracheal intubation is difficult using more conventional approaches. Based on our experience, we would like to expand on the recent letter of Dr. Hammer (1), because we feel that guided intubation is a technique that every medical practitioner and paramedic should learn as an alternative to traditional methods. It must be practiced in simple cases before attempting it in more difficult patients.

A reported problem with the Flexilum™ light (2), and one that we have personally encountered, is the separation of the bulb from the wire stylet. This is especially prone to happen if the stylet is reused over 30 times, as it may be (3). However, this problem now has been overcome after the manufacturers redesigned the device to incorporate a stronger light and to encase the bulb and wire in a plastic coating (Tube-Stat™, Concept Corporation, Clearwater, FL).

Three further points deserve mention. First, transillumination is, of course, much more effective when the room lights are turned down. Second, the angle of the bent stylet is crucial, being slightly greater than 90° if the head and neck are kept neutral; intubation appears easier if the head is maximally extended and the neck flexed by elevating the occiput on a pillow in the traditional "sniffing" position. Third, one of us (RTW) intubates 90% of his patients with this "guided" method or what is better described as an "indirect visual" intubation with the aid of the Airway Intubator (4). This device prevents lateral movement of the tube and resists the tendency for the tube to go posteriorly into the esophagus. We recommend these techniques for operating room, field, and emergency department intubations.

R. Tudor Williams, MD
Department of Anesthesiology
University of Calgary School of Medicine
Calgary, Alberta Canada T2N 4A9

Ronald D. Stewart, MD
Department of Anesthesiology
University of Pittsburgh School of Medicine
Pittsburgh, PA 15213

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In Vitro Degradation of Atracurium

To the Editor:

Atracurium, a nondepolarizing relaxant of intermediate duration, has the potential for spontaneous degradation by Hofmann elimination while also undergoing metabolism by plasma esterases. The relative role of each pathway in the in vitro degradation of atracurium in human plasma has recently been examined by Nigrovic et al. (1) and by us (2). Diametrically opposite conclusions were reached. Nigrovic et al. concluded that Hofmann elimination is the major route of atracurium degradation in humans; we concluded that ester hydrolysis is the major route of atracurium degradation (2). Although both groups of investigators approached this issue in a somewhat similar way, differences in methods and selection of enzyme inhibitors may explain the opposite conclusions.

We (3) and others (4) noted that the degradation of atracurium was several-fold faster in plasma than in buffer (at the same temperature and pH). Dilution of plasma with buffer slows the rate of degradation of atracurium. These findings suggest that a plasma constituent facilitates the degradation of atracurium. In subsequent experiments (2), we noted that degradation of atracurium and its monoquaternary alcohol metabolite and the subsequent formation of laudanosine were several-fold faster in pooled plasma than in buffer. More important, addition to plasma of diisopropylflurophosphate (DIFP) (3.0 μmol/ml) or tetraisopropylpyrophosphoramide, which are potent but nonspecific esterase inhibitors, markedly retarded the degradation of atracurium and formation of laudanosine to values seen with buffer alone. From the data obtained, we were able to estimate that about $\frac{2}{3}$ of atracurium is degraded by ester hydrolysis and $\frac{1}{3}$ by Hofmann elimination. Laudanosine is the major endproduct of both pathways.

More recently, in an attempt to characterize the esterases involved in atracurium metabolism, we evaluated the ability of acetylcholinesterase (EC 3.1.1.7), butyrlcholinesterase (EC 3.1.1.8), and carboxylic esterhydrolase (EC 3.1.1.1) in vitro to metabolize atracurium. These unpublished findings demonstrate that none of these esterases facilitates the degradation of atracurium. Nigrovic et al. (1) used tri-orthotolylphosphate (TOTP) to inhibit esterases, specifically carboxyesterase. If TOTP is a specific inhibitor of carboxyesterases, and if carboxyesterases do not metabolize atracurium, their in vitro findings in human plasma are not surprising. Thus the difference between their findings and ours may be related to the specificity or nonspecificity of the esterase inhibitors chosen. Recently, Ward et al. (5) demonstrated that significant plasma concentrations of both laudanosine and the monoquarternary alcohol occur within minutes after a bolus of atracurium to patients; minimal concentrations of the monoquarternary acrylate were noted. The monoquaternary alcohol is an immediate product of the ester hydrolysis pathway for atracurium—the major route of atracurium degradation.

D. Ryan Cook, MD
Richard Stiller, PhD
Michael Ingram, MD
Departments of Anesthesiology, Pharmacology, and Psychiatry
University of Pittsburgh School of Medicine
Pittsburgh, PA 15261

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Psychomotor Tasks and Recovery from Anesthesia

To the Editor:

In a recent article, Denis et al. (1) evaluated the reliability and validity of three psychomotor tasks as measures of recovery from anesthesia. The validity of the findings has since been questioned (2); I question their reliability.

Denis et al. examined psychomotor performance in an experimental group and in an unanesthetized control group over four test sessions (one session prior to anesthesia and three sessions after recovery from anesthesia). Their criterion for task reliability was that of invariant control-group performance over the four sessions, the implicit assumption being that performance that remains stable over time is free from training effects that would otherwise interact with, and obscure, anesthetic side effects. The authors concluded that only the "Track Tracer" task was reliable by this criterion.

However, readers should know that invariant performance is *not* a reliable indicator of the absence of training effects. In an ingenious study, File and Lister (3) have shown that, even where control performance of a task is invariant over time, the adverse effect of a drug (lorazepam) can still vary in inverse proportion to the amount of prior training. In other words, a drug may interact with a *masked training effect,* undetected by control performance, to give a misleading overestimation of the adverse influence of the drug (4). The study of File and Lister then raises the issue of what constitutes a training effect and uncertainty as to whether a pure performance measure is obtained on any task.

Consequently, one cannot unequivocally accept the conclusion of Denis et al. that their method of evaluation is indeed "reliable." The profile of their result is so similar to that of File and Lister that the markedly impaired performance of their experimental group in the session immediately after recovery from anesthesia could convincingly be ascribed to an interaction between the anesthetic and the relatively untrained state of performance (patients had experienced only one previous training session). Performance of a well-learned task may not have shown such gross impairment. Whither then the establishment of further criteria to assess "street fitness" (2)?

In conclusion, one should emphasize that although performance tests in humans offer the opportunity to make objective and sensitive measurements of the cognitive side effects of anesthesia, many extraneous factors unrelated to the immediate clinical conditions may also affect performance. Herbert (5) discusses such factors with specific reference to the application of human performance tasks to anesthesia, and readers are strongly referred to that paper.

Keith Millar, PhD
Behavioural Sciences Group
University of Glasgow Faculty of Medicine
Glasgow G12 8QQ
Scotland

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In Response:

The comments made by Millar refer to the definition of the reliability of a test, and he cites the results of File and Lister as a basis for his argument. File and Lister compared a group of subjects receiving first a placebo and then lorazepam with a group of subjects receiving lorazepam after baseline measurements. They concluded that "there are good correlations in the placebo treated subjects in all of the tests used, demonstrating the reliability of the various measures employed." Results would have been less ambiguous if they had demonstrated before the experiment the reliability of the tests they used with subjects who did not receive a placebo, because those subjects may show a placebo effect. Moreover, the sample from which they calculated the correlations between the tests was small ($n = 9$), and there was no apparent correction for ties when calculating P.

Millar uses the ambiguity that exists in the experiment of File and Lister as a basis for a "new" definition of the reliability of a test and hence the possible lack of reliability of the Track Tracer. This new definition of the reliability of a test may perhaps be useful when a placebo effect interacts with a training effect, but it should not be generalized. Millar seems to confound the interaction between a possible placebo effect and a training effect with the reliability of a test.

Millar also cites Herbert, who wisely suggested that "Poulton's preferred solution is to use the alternative, between-groups design. This strategy calls for one group of subjects to undergo the experimental condition while a second group provides control data. Both groups, of course, should be equated on all variables relevant to the experiment." Herbert enumerates these variables as being age, sex, and duration of induced unconsciousness. These variables have been controlled in our experiment. This course of action has been followed in our experiment in which two groups have been used. A control group has been measured in order to evaluate the reliability of the tests or the ability of the tests to give the same score for a subject on repeated testing. An experimental group has been measured to evaluate the validity of the tests or the degree to which the tests served the purpose for which they were intended.

Millar cannot refer to a "masked training effect" in our experimental group when subjects of our control group did not demonstrate a training effect. The interaction between a possible placebo effect and a training effect cannot be advocated when there is no placebo effect (subjects belonging to our control group received no placebo) nor training effect (the performance of the subjects belonging to our control group did not improve over four trials).

Millar should conduct specific experiments to demonstrate his hypothesis. The definition of the reliability of a test is discussed in many textbooks, usually in unambiguous terms (1).

R. Denis, MD
J. Letourneau, PhD
University of Montreal
Montreal, Quebec Canada

D. Londorf, MD
Grady Memorial Hospital
Atlanta GA 30329

Reference

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Are the Requirements for Hepatic Injury with Halothane and Enflurane in Rats Really Different?

To the Editor:

The exciting piece of work presented in a recent issue of *Anesthesia and Analgesia* (1) is devoted to a problem that has been occupying the minds of anesthesiologists during the last few years, i.e., whether halothane-induced hepatic injury in barbiturate pretreated hypoxic rats is due to reductive metabolites of halothane or to hepatic oxygen deprivation created by experimental conditions and respiratory and circulatory depression. The authors suggest that the pathogenesis of liver injury from halothane and enflurane is different; namely, pure hypoxic mechanisms for enflurane and reductive metabolism for halothane. If we accept the suggested interpretation, it would seem very difficult to answer an important question: why was halothane anesthesia not accompanied at the beginning by similar degrees of "hypoxic" liver damage as enflurane anesthesia? Halothane jeopardizes hepatic oxygen supply to a similar (2,3) or even greater (4,5) extent than enflurane. Therefore, if enflurane leads to liver damage by hypoxic mechanisms, halothane must lead to at least similar damage and thereafter, on the top of ischemic damage, halothane should have produced additional injury resulting from reductive metabolites. However, events were different. An alternative explanation to the data can be offered.

According to the experimental design, animals were exposed to different degrees of hypoxia (F_{IO_2} 0.14 for halothane and 0.10 for enflurane) and had different body temperatures (24–26° C for halothane and 31–32° C for enflurane) (Tables 4, 5). Animals anesthetized with enflurane were exposed to more severe hypoxia and had a greater oxygen requirement (resulting in a much lower oxygen supply–demand ratio) than animals exposed to halothane. Therefore it is not surprising that liver damage developed earlier and more severely in enflurane compared with halothane anaesthetized rats.

Table 5 shows that rats pretreated with phenobarbital (induced) demonstrated more severe liver damage than intact (noninduced) rats. The serum level of SGPT was greater in induced than in noninduced rats after 24 hr of exposure to halothane. These values were compared with serum SGPT observed immediately after exposure to enflurane. Why are the enflurane data at 24 hr not presented? What was the mortality rate in enflurane animals? A high mortality rate in enflurane treated animals would confirm that the enflurane treated rats were exposed to more severe hypoxia and therefore died earlier than halothane anesthetized animals.

The difference in serum SGPT values between enzyme-induced animals and noninduced rats reached statistical significance in halothane anesthetized animals but not in enflurane anesthetized or severely hypoxic rats (Table 5). Absence of significance does not mean significance of absence; besides, there were only four animals in the noninduced enflurane group. With a larger number of observations, the authors might also find a statistically significant difference in the enflurane group. Finally, there is a possibility that widespread metabolic effects of phenobarbital on the liver may include induction of SGPT. An artifact would result from comparing serum SGPT as a measure of hepatotoxicity in groups of animals having different endogenous liver SGPT activity.

Table 6 shows that halothane-exposed animals had similar serum SGPT activities, regardless of body temperature, whereas animals exposed to enflurane had greater serum SGPT activity when they were externally heated compared with hypothermic rats. These data do not prove that the mechanisms of liver damage during halothane and enflurane are different. The difference may be due to the possibility that the change in oxygen demand (induced by the difference in body temperature) was insufficient to change the hepatic oxygen supply–demand ratio to a degree required to cause liver damage in the halothane (moderately hypoxic) group, and was sufficient in the enflurane group, which had a much lower oxygen supply.

If the hepatic oxygen supply (including F_{IO_2} values) and other conditions (e.g., body temperature) were identical in both halothane and enflurane groups, the difference in patterns of hepatic injury could have been attributed to the difference in anesthetics per se, possibly their metabolism. In conclusion, the difference in the observed patters of hepatic injury after halothane and enflurane may also be attributed to different degrees of hepatic oxygen deprivation, without involvement of the reductive metabolism of halothane. The mystery of whether anesthesia-induced hepatic injury in the model is purely hypoxic, or a metabolically mediated event, remains to be solved.

Simon Gelman, MD, PhD
Department of Anesthesiology
University of Alabama at Birmingham
Birmingham, AL 35294

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In Response:

The purpose of our work (1) was to compare what appear to be two very different rat models of anesthetic related hepatotoxicity: the halothane-hypoxia model, which was originally introduced by our laboratory (2,3,4), and the recent model of Shingu, et al. (5,6). In the Shingu model, all anesthetics have been proposed to be hepatotoxic via hypoxic/anoxic mechanisms. Without a complete comparison between the two models (7), these authors suggested that the halothane-hypoxia rat model also produced hepatic necrosis as a result of hypoxia/anoxia. Characterizing the Shingu model and comparing it with our halothane model was the difficult task of our current publication (1). Due to the numerous comparisons required and the complexity of the data, some confusion over the results is not surprising. We will attempt to address Dr. Gelman's questions in the order in which they appear in his letter.

Dr. Gelman asks why halothane anesthesia was not accompanied by similar degrees of "hypoxic" liver damage as enflurane anesthesia. The reason is due to the differences in the exposure conditions under which the anesthetics were administered. As Dr. Gelman states, the enflurane exposure (under the conditions of the Shingu model) was carried out under lower oxygen tensions (10% O_2 versus 14% O_2 for our halothane model), and the animals were heated to maintain near normothermia (whereas the halothane exposed animals were not). Because differing exposure conditions were used, a comparison of which anesthetic more greatly jeopardizes liver blood flow is not valid. The less stressful conditions of the halothane–14% O_2 exposure did not produce the hallmarks of "hypoxic/anoxic" liver damage: watery vacuolization of centrilobular hepatocytes and elevated serum enzymes immediately after exposure (8,9). Nonetheless, hepatic necrosis develops gradually over the next 12–24 hr in the halothane–14% O_2 model.

The purpose of Table 5 was not to demonstrate that phenobarbital induction of hepatic drug metabolizing enzymes leads to more severe liver damage than in noninduced rats, but rather that enzyme induction was required for the production of *any* hepatic necrosis in halothane-exposed animals, while not being necessary to produce the hypoxic/anoxic liver injury observed in the Shingu model. Enflurane data at 24 hr are not shown because we chose time points most indicative of the type of hepatotoxicity produced in the particular model being studied.

In our hands, the mortality during exposure of the animals subjected to enflurane under the conditions of the Shingu model averaged approximately 25%. The chance of a death occurring during a halothane–14% O_2 exposure is much less (approximately 10% or less). This is further testament to the severity of exposure conditions in order for the Shingu model to produce hepatic injury. Of all animals that did survive the anesthesia periods, none died sooner than when the investigators saw fit to kill them.

In further questioning the data in Table 5, Dr. Gelman also raises a point as to the statistical significance of the enflurane data. Whether any differences could be found in SGPT values between phenobarbital pretreated and nonpretreated rats after the enflurane exposures is totally incidental. The purpose of the data was to provide a *qualitative* comparison of the two models. We agree that having only four animals in an experimental group does not provide good statistical significance. Statistical analysis was provided at the request of reviewers of the work. Although Dr. Gelman speculates that phenobarbital pretreatment may induce hepatic GPT levels, he provides no references to support this contention. Nor are we aware of any.

Also questioned are the results in Table 6, which pertain to the requirement of maintaining body temperature during anesthetic exposure for the subsequent development of hepatotoxicity in the two models. Halothane-anesthetized animals developed a similar degree of hepatic injury whether or not normal body temperature was maintained during the exposure period. External heating (maintenance of body temperature) was required for the development of hepatotoxicity in the Shingu model. The halothane–14% O_2 exposed animals *did not* develop hypoxic liver injury, as serum enzymes and morphology were normal immediately after exposure. On the other hand, exposure of rats to enflurane under the conditions of Shingu et al. (5,6) did.

In response to the speculation over using similar exposure conditions for the two anesthetics, previously published work (10) has shown that when enflurane is administered under conditions identical to the halothane–14% O_2 model, no hepatotoxicity develops.

In our minds, differences between two animal models in pretreatment requirements and exposure conditions necessary to produce a hepatic lesion, and the time course of development of the resulting lesion, are indicative of differing mechanisms of anesthetic-induced liver injury. Because the hallmarks of "hypoxic/anoxic" liver injury are not present in the halothane–hypoxia rat model, it would seem that other mechanisms must be at work.

In closing, it seems appropriate to put these debates over the mechanisms of anesthetic-related hepatotoxicity in rats in perspective. The extensive pretreatments and harsh exposure conditions required to produce a hepatic lesion (in males only), as well as the mildness and short duration of that lesion, are quite dissimilar from even the mild, acute hepatic dysfunction resulting in humans after halothane anesthesia (11,12). Recently, another animal model of halothane-associated hepatotoxicity utilizing guinea pigs has been presented (13,14). No pretreatments are required. Hepatic necrosis results even after exposures at high oxygen tensions. Both sexes are susceptible. The lesion develops over 48 hr and involves an extensive fatty infiltration of hepatocytes, as well as a frank necrosis of centrilobular hepatocytes. The necrosis requires 7 days or more to resolve. Certainly, regardless of mechanisms, this guinea pig model should provide a more realistic tool in investigating the anesthetic related hepatic dysfunction observed in humans.

Richard C. Lind, MS
A. Jay Gandolfi, PhD
Burnell R. Brown Jr, MD, PhD
Department of Anesthesiology
University of Arizona Health Sciences Center
College of Medicine
Tucson, AZ 85724

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Book Reviews

Textbook of Pain

Patrick D. Wall and Ronald Melzack, eds. Edinburgh: Churchill Livingstone, 1984, 866 pp, $105.00.

The first major texts on this subject were published in the 1950s: *The Management of Pain,* by J. Bonica (1953); *Pain, Its Mechanism and Control,* by J. White and W. Sweet (1955); and *Pain,* by W. Noordenbos (1959). The subject of pain received a major stimulus with the publication of the Melzack and Wall's *Gate Theory of Pain* in 1965 and with the founding of the International Association for the Study of Pain (IASP) in 1974. A veritable explosion of new knowledge of pain and its treatment followed these events. Much previous knowledge was proved incorrect, treatments were disguarded, and indeed a whole new concept of pain emerged.

In the introductory chapter of *Textbook of Pain,* Patrick Wall notes the changing attitude to pain: from "Pain is that sensory experience evoked by stimuli that injure" (Mountcastle 1968), to "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP 1979). This definition indicates the need for evaluation and treatment of both physical and psychologic aspects of pain. Thus it comes as no surprise that *Textbook of Pain* aims to bring together a large body of information from both basic and clinical sciences and from many medical specialties. In this respect the book differs from a number that have been published in recent years, which emphasize particular aspects of pain. Bias from any one specialty is studiously avoided. Contemporary medicine is presented alongside some surviving but questionable approaches based on outdated naive concepts. "The intention of this book has been to present all of the major attitudes to pain and its treatment." A formidable task! However, in the opinion of this reviewer, no prior text has achieved this task with anywhere near the success of *Textbook of Pain.*

A textbook is "a standard source of reference, and a systematic representation of the principles and vocabulary." *Textbook of Pain* meets this definition well. It contains 866 pages with 79 chapters plus a prologue (by W. Noordenbos), an introduction, and final summary (by P. Wall). The text is divided into three parts: Basic Aspects, Clinical Aspects of Diseases in which Pain Predominates, and Therapeutic Aspects. The 102 contributors make up a virtual "Who's Who" of basic scientists and clinicians in the field of pain.

Wall and Melzack have made major contributions to basic science aspects of pain that have had very important clinical implications. This has given them excellent perspective, which is evident in their choice of contributors to Section 1. To help formulate and edit the two clinical sections, the editors have drawn upon Clinical Consultants: J. Bonica (Anesthesiology), H. Merskey (Psychiatry), P. Nathan (Neurology), J. O'Brien (Orthopedics), W. Sweet (Neurosurgery), and C. Wynn Parry (Rehabilitation). Each of these contributors also contributes chapters about fields in which they are all acknowledged authorities.

Most of the chapters in this text are good, the only limitation being one of length and depth of coverage. This is inevitable with the number of topics covered. Fortunately, the caliber of most authors is such that they are able to give an authoritative "distillation" of the current state of the art in their field. Adequate key references are then given, with emphasis on reviews and useful monographs. The introductory chapter by Wall gives a masterly overview of current concepts of pain, introducing chapters that follow. In Section 2 (Clinical Aspects), headings include "Peripheral Damage," "Deep and Visceral Pain," "Nerve and Root Damage," "Carcinoma" (including "Hospice Care"), "Central Pain," and "Pain and Psychological Medicine." In Section 3 (Therapeutic Aspects), a wide perspective is taken with the objective of encouraging the pain therapist to consider the many options now available. Headings include: "Pharmacology," "Local Blockade," "Lesions," "Stimulation," "Physical Therapy," "Radio- and Chemo- therapy," and "Psychotherapy." Details of how-to are not the aim of most chapters, so appropriate references are provided.

Among this feast of valuable information one could expect to find at least some weak areas. The text implies by its title that it is concerned with all pain, including acute pain. Indeed, several chapters deal with this topic to some degree. However, the pathophysiology, sequelae, and treatment of acute pain receive much less emphasis than is accorded to chronic pain. In this reviewer's opinion, this is not a major criticism because there are several good texts on acute pain but few, if any, balanced texts on chronic pain.

In his prologue, Noordenbos notes that "anesthetists, who by virtue of their skill in combating the acute predictable pain as a result of surgery, consider themselves fit to face that formidable foe which is chronic pain." However, in the summary Wall says that "the reader will sense that there is a great expansion of effort, knowledge and hope

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. . . some disciplines such as Anesthesiology are in a rapid evolution." This book contains much information to help anesthesiology contribute to knowledge and treatment of pain. Hopefully it will help anesthesiology, or any other speciality, to avoid earning Wall's timely comment that "every society contains its myopic mechanics and plumbers who usefully tinker with their favourite bit of machinery, unable to detect the whole beyond the part." Wall and Melzack's *Textbook of Pain* gives the reader a view of the whole. It should be in every medical library. No basic scientist or clinician involved in the field of pain can afford to be unfamiliar with the broad scope of material presented in this text.

Michael J. Cousins
Professor and Chairman
Department of Anaesthesia and Intensive Care
Flinders Medical Centre
Adelaide, Australia

The Pregnant Surgical Patient

Jeffrey M. Baden and Jay B. Brodsky, eds. Mt. Kisco, NY: Futura Publishing Co., 1985, 260 pp, $36.00

When anesthesia and surgery become necessary during pregnancy, extraordinary risks for the mother and conceptus are presented. The emergent nature of most surgical procedures in pregnancy, coupled with sparse and relatively inaccessible data on early gestational effects of anesthesia and surgery in the human, often impedes the formulation of a preferred plan of management of the patient care team. Thus anesthesiologists, surgeons, and obstetricians alike should welcome the addition of a comprehensive text on the subject.

In the introduction to *The Pregnant Surgical Patient*, the editors point out that this volume intends to "bridge the gap between specialties by providing the reader with an overall perspective of the pregnant surgical patient." In this respect, they have accomplished their mission. The book reviews much information presently available and pertinent to the anesthesiologist while including chapters of interest for the obstetrician and surgeon. However, in attempting to cover the multidisciplinary approach to patient care, the text will likely disappoint the anesthesiologist or anesthetist who anticipates an in-depth treatise on the subject. For example, the book minimally addresses preoperative management by the anesthesiologist and makes few specific recommendations about the conduct of general anesthesia, peripheral nerve blocks, or various monitoring methods. Little is written about possible postoperative methods for alleviation of pain. These omissions may result in part from space limitations imposed by the relatively small size of the book, whose pages measure 14.5 × 22.5 cm.

Authored primarily by faculty members at Stanford University, ten chapters emphasize three areas of concern: 1) principles of teratology and teratogenic effects of anesthetic agents; 2) physiology of pregnancy and possible effects of anesthetics on maternal physiology; and 3) practical aspects in the diagnosis, incidence, and clinical management of surgical conditions in pregnancy. Most chapters are informative, concise, and abundantly referenced, and are presented in a reasonably pleasant style. Yet several chapters tend to befuddle the reader by inclusion of excessive statistical data within the text. Additional tables or figures seem indicated. Some repetition among chapters, misspelled words, and typographical errors also tend to diminish the quality of the book.

Of marginal value to the anesthesiologist, and probably of greater interest to the surgeon, is chapter 5, "Physiologic Effects of Drugs used in Anesthesia." The discussion on placental blood flow and fetal physiology seems rather brief considering the recent appearance of exciting studies in this area. The pharmacologic profile of individual anesthetic drugs contains basic information already known by most anesthesiology residents. Several discussions on vasopressors and uterine blood flow exclude recent studies on more commonly used drugs such as dopamine and dobutamine. This reviewer found Chapter 7, "Surgical Resolution of Non-Obstetric Abdominal Crises," to be particularly delightful and original. The next chapter, "The Pregnant Surgical Patient," contains a lengthy discussion on surgical endocrinology and cancer during pregnancy but overlooks pregnancies complicated by neurologic, orthopedic, and cardiac procedures. Several chapters contain material that appears to be out of context or, at least, at variance with the objectives of the manuscript.

In the final chapter, the author presents information on fetal outcome after anesthesia and surgery. The discussion utilizes data from relatively old, retrospective studies and concludes that there is no definitive evidence that any anesthetic drug or technique is safer as long as maternal blood pressure, ventilation, and oxygenation are kept within normal limits, suggesting that the choice of anesthesia matters little when the anesthesia team avoids hypoxia and hypotension. This notion will not be accepted by many anesthesiologists who must rely heavily on experience and intuition when developing a sound management plan. This book would have concluded more effectively had the author used his experience to provide specific anesthetic recommendations. As it stands, however, the closing chapter leaves the reader somewhat confused and perplexed.

In summary, *The Pregnant Surgical Patient* successfully fosters a multidisciplinary approach to patient care. Due to its incompleteness and the omission of important subject matter, the book fails to serve as a valuable reference source. It appears best suited for the practitioner with limited experience in the management of obstetric patients or surgery during pregnancy and, for substantial benefit, must be read in its entirety.

A. Scott Wheeler, MD
Associate Professor of Anesthesiology
Department of Anesthesiology
University of Alabama at Birmingham
Birmingham, AL 35234

Atlas of Regional Anesthesia

Jordan Katz, MD. Norwalk, CT: Appleton-Century-Crofts, 1985, 203 pp, $75.00.

The administration of safe and effective regional anesthesia requires an intimate knowledge of the anatomy and neuroanatomy of the areas to be blocked and of the sites of needle insertion. The *Atlas of Regional Anesthesia* will provide the resident with an excellent reference from which to plan his nerve block procedures, and the experienced practitioner will refresh his or her memory of the anatomy and techniques of blocks which are infrequently done. This volume is an atlas and instructional manual of regional anesthetic procedures and succeeds in presenting the techniques "in as simple and straightforward a manner as possible," as mentioned in the Introduction. Dr. Katz addresses some of the important aspects of clinical management of regional blocks in a few brief paragraphs entitled "Indications for Nerve Blocks, Preparation of the Patient, Local Anesthetics, Neurolytics, and Aids to Nerve Blockade." These important subjects are succinctly addressed in just over two pages, implying to the reader that the subjects will not be emphasized unless specific procedures carry unique hazards.

All of the commonly used regional block procedures and most of those less frequently used are included in the 94 techniques presented. The anatomy and technique for each block are presented on a single page with the procedure illustrated on the opposite, facing page. The reader is not forced to hunt through text to locate the illustration to match the description, as in most textbooks of regional anesthesia. This format is uniform throughout the book, even though many of the brief descriptive paragraphs leave at least half of the page empty. A list of the risks or complications peculiar to each block might have been added to these half-blank pages. The descriptions of anatomy and technique are uniformly succinct and accurate with rare errors. As an example, the femoral nerve is described as originating from "the posterior divisions of the second, third and fourth lumbar segments," rather than the dorsal divisions of the anterior rami of these nerves. The descriptions of the brachial plexus and of spinal and epidural anatomy are especially well-written in the direct, lucid style that distinguishes the book.

The lengths of needles and almost all measurements of anatomical landmarks are described in inches rather than in metric notations. This is an unfortunate departure from the current standard in medical literature, which may cause inconvenience to anesthesiologists who learned the metric system as their national standard and to those of us who have converted to it.

The illustrations are outstanding in their clarity and accuracy, matching the excellence of the text in demonstrating the regional block procedures. John W. Brown reveals himself to be a supurb medical illustrator and an artist of unusual talent. Inaccuracies are very rare, although the positions of patients' heads and necks are incorrectly depicted turned to the side, rather than in the neutral position, for blocks of the glossopharyngeal and vagus nerves and the superior laryngeal nerve.

The atlas is a handsome hard-cover volume, 21.5 × 28.2 cm (8½ × 11 inches), with excellent-quality glossy paper. The elegance of the volume intimidated me to curtail my usual notemaking in the margins or in the generous spaces below descriptions, in order to avoid spoiling the fine features of the book. The cost of this text is not surprising, given the plethora of colored illustrations and the quality of the printing and binding.

The excellence of the text and illustrations and the convenience of having each procedure's description immediately opposite the drawings will appeal to most anesthesiologists. It is a volume that should be included in all hospital and departmental libraries, as well as those of anesthesiologists who frequently employ block anesthesia, where it will be a valuable adjunct to the texts and handbooks devoted to regional anesthesia.

James C. Erickson III, MD
Professor of Clinical Anesthesia
Northwestern University Medical School
Chicago, IL 60611

Books Received

Receipt of the following books from their publishers is acknowledged with thanks. Selected books from this list will be reviewed in the future.

Advances in Anesthesia, Volume 3. R.K. Stoelting, P.G. Barash, T.J. Gallagher, eds. Chicago: Yearbook Medical Publisher, 1986, 403 pp, $55.95.

Anaesthesia—Innovations in Management. R. Droh, W. Erdman, R. Springte, eds. New York: Springer Verlag, 1985, 236 pp, $31.50.

Anesthesia for Ambulatory Surgery. B.V. Wetchler, ed. Philadelphia: Lippincott, 1985, 476 pp, $55.00.

Anesthesia in the Elderly. H.T. Davenport. London: W. Heinemann Medical Books, Ltd., 1985, 200 pp, $16.00.

Introduction to Anesthesia: Principles of Safe Practice. R.D. Dripps, J.E. Eckenhoff, L.D. Vandam. Philadelphia: W.B. Saunders, 1982, 496 pp, $24.50.

A Practice of Anesthesia for Infants and Children. J.F. Ryan, I.D. Todres, C.J. Cote, N. Goudson-Zian. Orlando, FL: Grune & Stratton, 1985, 314 pp, $67.50.

TRACRIUM® INJECTION (atracurium besylate)

Intrinsically predictable, uncommonly flexible

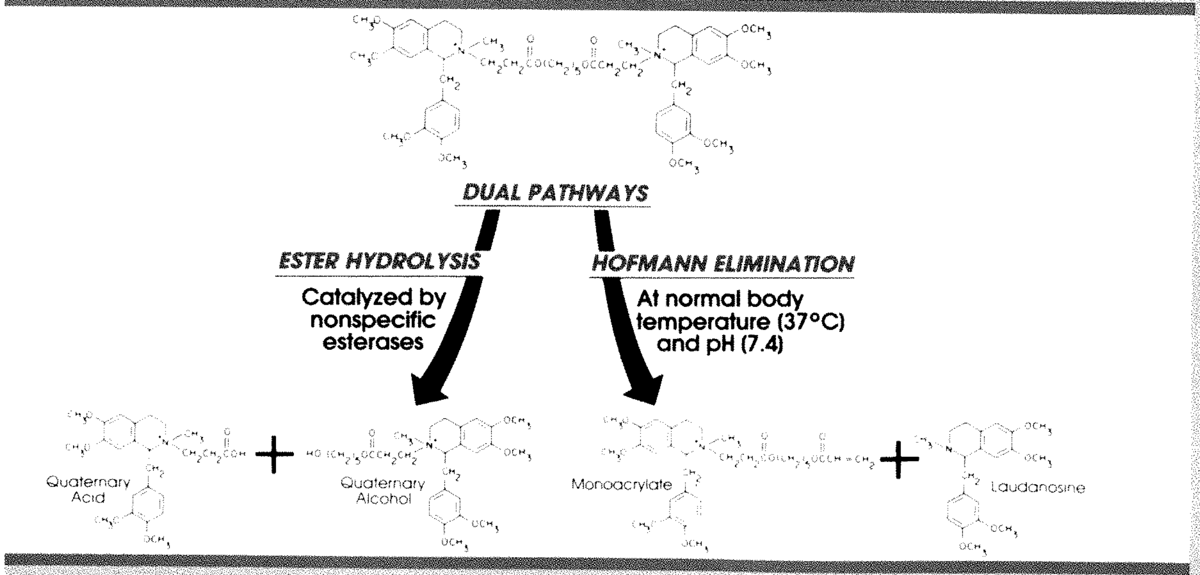
- **Predictable because it doesn't accumulate.**

Equal maintenance doses of Tracrium, repeated at equal time intervals during surgery, have no cumulative effect on recovery time.

Once recovery begins following the last administered dose, it is relatively rapid and independent of the total dose. Thus, you need not calculate progressively smaller doses of Tracrium for repeat administration. Recovery is more consistent and predictable.

- **Metabolized independent of liver or kidney function.**

Tracrium® Injection (atracurium besylate) is not dependent on kidney or liver function for elimination. It is inactivated by two nonoxidative pathways:



- **Few cardiovascular effects.**

  At recommended doses, Tracrium produces virtually no clinically significant cardiovascular hemodynamic effects – an advantage over tubocurarine, metocurine, and pancuronium in patients with compromised cardiac ability or cardiac risk.

- **Minimal histamine release at recommended doses.**

  Tracrium Injection is a less potent histamine releaser than d-tubocurarine or metocurine.

  Clinically significant changes (about 200% of control) in arterial pressure and heart rate resulting from histamine release occur well within the clinical dosage range (at ED_{95}) for curare, at the upper limits of the clinical dosage range (at 2 x ED_{95}) for metocurine, and outside the clinical dosage range (at 3 x ED_{95}) for atracurium.[1]

- **No mixing. Ready to use.**

  Good stability.

  Tracrium is easily administered, requiring no premixing or measuring. At room temperature (25°C), potency loss is 5% per month.

Multiple-dose vials can reduce the amount of Tracrium subject to waste by as much as 22% when compared to ampules!*

*Data on file, Burroughs Wellcome Co.

Gives you superior control and predictability

TRACRIUM® INJECTION

(atracurium besylate)

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

Reference:
1. Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, and d-tubocurarine, abstracted. Anesthesiology 1982;57:A261.

Please see brief summary of prescribing information on following page.

TRACRIUM® INJECTION
(atracurium besylate)

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

DESCRIPTION: Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:
General: Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine. The possibility of substantial histamine release in sensitive individuals must be considered however. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. Atracurium was evaluated in a battery of three short term mutagenicity tests. It was non-mutagenic in both the Ames Salmonella assay at concentrations up to 1000 μg/plate, and in a rat bone marrow cytogenicity assay at up to paralyzing doses. A positive response was observed in the mouse lymphoma assay under conditions (80 and 100 μg/ml, in the absence of metabolic activation) which killed over 80% of the treated cells; there was no mutagenicity at 60 μg/ml and lower, concentrations which killed up to half of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations (1200 μg/ml and higher) which also killed over 80% of the treated cells. Mutagenicity testing is intended to simulate chronic (years to lifetime) exposure in an effort to determine potential carcinogenicity. Thus, a single positive mutagenicity response for a drug used infrequently and/or briefly is of questionable clinical relevance.

Pregnancy: *Teratogenic Effects:* Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 2 years have not been established.

ADVERSE REACTIONS: Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

Approximately one million patients received Tracrium during the first year following introduction to the U.S. market in December, 1983. Spontaneously reported adverse reactions were uncommon (approximately 0.02%). The following adverse reactions are among those most frequently reported, but there are insufficient data to support an estimate of their incidence:
Musculoskeletal: Inadequate block, prolonged block
Cardiovascular: Hypotension, vasodilatation (flushing), tachycardia, bradycardia
Respiratory: Dyspnea, bronchospasm, laryngospasm
Integumentary: Rash, urticaria, reaction at injection site.

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended following the use of succinylcholine for intubation under balanced anesthesia.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.6 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

NEW!
10 ml Multi-Dose Vial

now available for

TRACRIUM® INJECTION
(atracurium besylate)

- **Convenient**
- **Economical**
- **Uniquely Identifiable**

An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for patients with significant cardiovascular disease and for patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated.

No Tracrium dosage adjustments are required for patients with renal disease or for pediatric patients two years of age or older. In pediatric patients, maintenance doses may be required with slightly greater frequency than in adults.

HOW SUPPLIED: Tracrium Injection, 10 mg atracurium besylate in each ml. Ampuls of 5 ml (50 mg atracurium besylate per ampul). Box of 10 ampuls (NDC-0081-0940-10).

10 ml Multiple Dose Vial (100 mg atracurium besylate per vial). The multiple dose vial contains 0.9% benzyl alcohol added as a preservative. Box of 10 (NDC-0081-0940-95).

Store under refrigeration at 2° to 8°C (36° to 46°F); DO NOT FREEZE.

U.S. Patent No. 4179507

Printed in U.S.A.

TRACRIUM INJECTION
(atracurium besylate)

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

85TRA11

Anesthesia and Analgesia

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Anaquest

introduces

Enlon®

(edrophonium chloride
injection, USP)

A rapid-acting
neuromuscular reversal agent

From the developers of
Ethrane® (enflurane) **and Forane®** (isoflurane)

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A Division of BOC Inc

60-second reversal
of neuromuscular blockade

- **Onset of reversal significantly faster than with neostigmine or pyridostigmine**—60 seconds versus 7 minutes for neostigmine, 12 minutes for pyridostigmine.[1,2]
- **Duration of reversal comparable to that of neostigmine**—66 minutes versus 76 minutes for neostigmine.[1,2*]
- **Significantly fewer muscarinic side effects and lower atropine requirement than with neostigmine**—edrophonium, 0.5 mg/kg, with only 7 μg/kg atropine, produced minimal change in heart rate or mean arterial pressure compared to noticeable changes in both indexes following neostigmine, 0.04 mg/kg, using *twice* the atropine dose (15 μg/kg).[1,2]
- **May be the preferred reversal agent for atracurium and vecuronium**
  "...compared with neostigmine, edrophonium has a more complete spectrum of atracurium reversal characteristics, and...antagonizes more rapidly residual atracurium-induced neuromuscular blockade."[3]

  "Edrophonium may in fact be the preferred reversal agent for routine use with [vecuronium], having the advantages that restoration of voluntary muscle function is very rapid, and that the relatively small dose of atropine required minimizes the unwanted side-effects of this drug."[4]

***Note:** When duration of action is adjusted for differences in onset of action, the relative durations are 65 minutes for edrophonium and 69 minutes for neostigmine.

1. Cronnelly R, Morris RB, Miller RD: Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. Anesthesiology 57:261-266, 1982. 2. Miller RD, et al: Comparative times to peak effect and duration of action of neostigmine and pyridostigmine. Anesthesiology 41:27-33, 1974. 3. Jones RM, Pearce AC, Williams JP: Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. Br J Anaesth 56:453-457, 1984. 4. Baird WLM, Bowman WC, Kerr WJ: Some actions of ORG NC45 and of edrophonium in the anaesthetized cat and in man. Br J Anaesth 54:375-385, 1982.

Please see use information on next page.

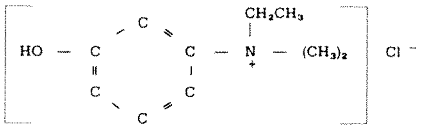
Anaquest

introduces

Enlon® (edrophonium chloride injection, USP)

DESCRIPTION

ENLON (edrophonium chloride injection, USP) is a rapid acting cholinergic (cholinesterase inhibitor). Chemically edrophonium chloride is ethyl (m-hydroxyphenyl) dimethylammonium chloride and its structural formula is:



ENLON contains in each mL of sterile solution:

10 mg edrophonium chloride compounded with 0.45% phenol and 0.2% sodium sulfite as preservative, buffered with sodium citrate and citric acid. Its pH is adjusted to approximately 5.4.

CLINICAL PHARMACOLOGY

ENLON (edrophonium chloride injection, USP) activates neuromuscular transmission primarily by inhibiting or inactivating acetylcholinesterase. By inactivating the acetylcholinesterase enzyme, acetylcholine is not hydrolyzed by acetylcholinesterase and is thereby allowed to accumulate. The accumulation of acetylcholine at the sites of cholinergic transmission facilitates transmission of impulses across the myoneural junction.

INDICATIONS AND USAGE

ENLON (edrophonium chloride injection, USP) is recommended as a reversal agent or antagonist of nondepolarizing muscle relaxants such as tubocurarine, metocurine, atracurium, vecuronium, or pancuronium. It is not effective against depolarizing relaxants such as succinylcholine and decamethonium. It is also useful if used adjunctively in the treatment of respiratory depression caused by curare overdosage. ENLON is recommended for use in the differential diagnosis of myasthenia gravis. It may also be used as an adjunct to evaluate treatment requirements of the disease, and for evaluating emergency treatment in myasthenic crisis. It is not recommended for maintenance therapy in myasthenia gravis.

CONTRAINDICATIONS

ENLON (edrophonium chloride injection, USP) is not to be used in patients with known hypersensitivity to anticholinesterase agents, or in patients having urinary obstructions of mechanical type.

WARNINGS

It is recommended that 1 mg atropine sulfate should be made available for immediate use, to counteract any severe cholinergic reaction. ENLON (edrophonium chloride injection, USP) should be used with caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Isolated instances of cardiac and respiratory arrest following administration of edrophonium chloride have been reported. It is postulated that these are vagotonic effects.

PRECAUTIONS

General: As with any antagonist of nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance. Should a patient develop "anticholinesterase insensitivity" for brief or prolonged periods, the patient should be carefully monitored and the dosage of anticholinesterase drugs reduced or withheld until the patient again becomes sensitive to them.

Drug Interactions: The drug should not be administered prior to the administration of any nondepolarizing muscle relaxants. The drug should be administered with caution to patients with symptoms of myasthenic weakness who are also on anticholinesterase drugs. Anticholinesterase overdosage (cholinergic crisis) symptoms may mimic underdosage (myasthenic weakness) so the use of this drug may worsen the condition of these patients (see OVERDOSAGE section for treatment).

Pregnancy Category C: It is not known whether ENLON (edrophonium chloride injection, USP) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, since there have been no adequate and well controlled studies in humans.

Labor and Delivery: The effect of ENLON on the mother and fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary is not known. The effect of the drug on the later growth, development and functional maturation of the child is also unknown.

Nursing Mothers: The safety of ENLON during lactation in humans has not been established.

ADVERSE REACTIONS

A patient in myasthenic crisis, being treated with ENLON (edrophonium chloride injection, USP) should be observed for bradycardia or cardiac standstill and cholinergic reactions if an overdosage is given. Reactions common to anticholinesterase agents such as edrophonium chloride are:

Cardiovascular: arrhythmias (especially bradycardia), fall in output leading to hypotension;

Respiratory: increased tracheobronchial secretions, laryngospasm, bronchiolar constriction and respiratory muscle paralysis;

Neurologic: convulsions, dysarthria, dysphonia, and dysphagia;

Gastrointestinal: nausea, vomiting, increased peristalsis, increased gastric and intestinal secretions, diarrhea, abdominal cramps;

Musculoskeletal: weakness and fasciculations;

Miscellaneous: increased urinary frequency, diaphoresis, increased lacrimation, pupillary constriction, diplopia, and conjunctival hyperemia.

OVERDOSAGE

Muscarine-like symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions and bradycardia) may appear with overdosage (cholinergic crisis) of ENLON (edrophonium chloride injection, USP) but may be managed by the use of atropine. Obstruction of the airway by bronchial secretions can arise and may be managed with suction (especially if tracheostomy has been performed) and by the use of atropine. Signs of atropine overdosage such as dry mouth, flush and tachycardia should be avoided as tenacious secretions and bronchial plugs may form. Should edrophonium chloride overdosage occur:

1. Maintain respiratory exchange.
2. Monitor cardiac function.

Appropriate measures should be taken if convulsions or shock are present.

DOSAGE AND ADMINISTRATION

The recommended adult intravenous injection for antagonism of neuromuscular block:

Administer 1 mL (10 mg) slowly within a period of 30 to 45 seconds, the dosage may be repeated to a maximum total dose of 4 mL (40 mg). Its onset of action is manifest within 30 to 60 seconds after injection. Response should be monitored carefully and assisted ventilation should always be employed. When given to counteract muscle relaxant overdosage, the dose effect on respiration should be observed prior to repeat dosages and assisted ventilation should be employed.

ENLON (edrophonium chloride injection, USP) Test in Differential Diagnosis of Myasthenia Gravis:

Adults:

Intravenous Dosage: Prepare a tuberculin syringe with 1 mL (10 mg) of ENLON and an intravenous needle; intravenously inject 0.2 mL (2 mg) within 15 to 30 seconds. The needle should be left in situ. If a cholinergic reaction (muscarinic side effects, skeletal muscle fasciculations and increased muscle weakness) occurs, discontinue test and intravenously administer 0.4 mg to 0.5 mg atropine sulfate. Inject the remaining 0.8 mL (8 mg) only if no reaction occurs after 45 seconds. The test may be repeated after one-half hour.

Intramuscular Dosage: Intramuscularly inject 1 mL (10 mg) of ENLON. If hyperreactivity (cholinergic reaction) is demonstrated, retest the patient after one-half hour with another intramuscular injection of 0.2 mL (2 mg) ENLON. This will eliminate the possibility of false-negative reactions.

Children:

Intravenous dose in children weighing up to 75 pounds:

Intravenously inject 0.1 mL (1 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 0.5 mL (5 mg). The recommended dose in infants is 0.05 mL (0.5 mg).

Intravenous dose in children weighing above 75 pounds:

Intravenously inject 0.2 mL (2 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 1 mL (10 mg).

Intramuscular Dose: Intramuscularly inject 0.2 mL (2 mg) ENLON in children weighing up to 75 pounds; above this weight, the dose is 0.5 mL (5 mg). All signs of hyperreactivity (cholinergic reaction) noted in the intravenous test will be demonstrated in the intramuscular test; however, there is a two to ten minute delay before reaction.

ENLON (edrophonium chloride injection, USP) Test to Evaluate Treatment Requirements in Myasthenia Gravis:

The test dose of ENLON should follow one hour after oral intake of the drug being used to treat the disease. The recommended dose is 0.1 mL to 0.2 mL (1 mg to 2 mg) administered intravenously. Response to ENLON test dose in treated myasthenic patients is summarized as follows:

Undertreated patient: Myasthenic response; characterized by increased muscle strength (ptosis, diplopia, dysphonia, dysphagia, dysarthria, respiration, limb strength). This indicates inadequate treatment of the myasthenic condition.

Controlled patient: Adequate response; characterized by no change in muscle strength with minimal side reactions (lacrimation, diaphoresis, salivation, abdominal cramps, nausea, vomiting, diarrhea). Fasciculations (orbicularis oculi, facial muscles, limb muscles) may or may not occur. The response indicates that therapy is stabilized.

Overtreated patient: Cholinergic response; characterized by decreased muscle strength and severe side reactions. Fasciculations may be observed. This response occurs in myasthenics who have been overtreated with anticholinesterase drugs.

ENLON (edrophonium chloride injection, USP) Test in Crisis:

Crisis in the myasthenic patient is characterized as a state of severe respiratory distress with inadequate ventilatory exchange, and unpredictable response to medication. If the patient is apneic, achieve ventilatory exchange immediately to avoid cardiac arrest and irreversible central nervous system damage.

The ENLON Test should not be conducted until respiratory exchange is maintained. The cholinergic patient will exhibit further weakness in the muscles of respiration and will have increased oropharyngeal secretions if ENLON is administered. Whereas, upon administration of ENLON the myasthenic patient will demonstrate improved respiration and can be given additional medication. To perform the test prepare a syringe with 0.2 mL (2 mg) ENLON and intravenously inject 0.1 mL (1 mg). The patient's cardiac and respiratory actions should be observed for change. The remaining 0.1 mL (1 mg) may be injected after one minute if no response is noted. If, after the entire 0.2 mL (2 mg) dose has been injected, no improvement in respiration occurs, discontinue all anticholinesterase drugs. Controlled ventilation can be achieved by tracheostomy with assisted respiration.

HOW SUPPLIED

ENLON (edrophonium chloride injection, USP):

NDC 10019-873-15 15 mL multidose vials.

2-85

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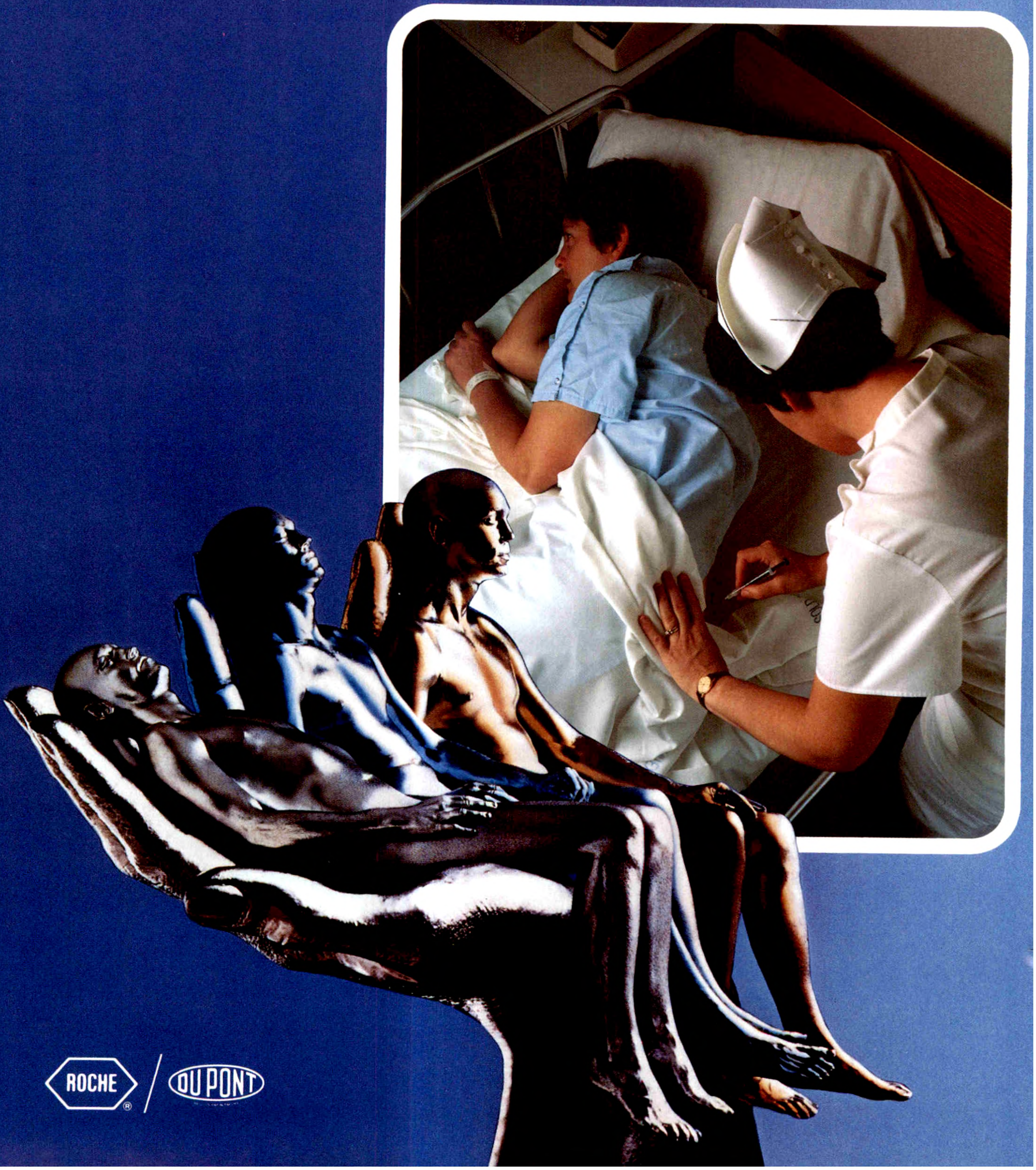

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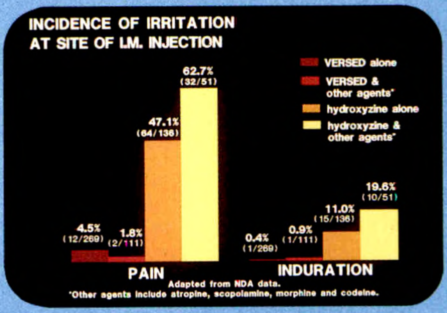


INCIDENCE OF IRRITATION AT SITE OF I.M. INJECTION

Adapted from NDA data.

*Other agents include atropine, scopolamine, morphine and codeine.

Sedates faster

In double-blind premedication studies, onset of sedation was significantly faster and more pronounced with VERSED I.M. than with hydroxyzine I.M. After 15 minutes, 43% of 149 patients treated with VERSED had reached the most desirable levels of sedation compared to only 19% of 101 patients treated with hydroxyzine.

Diminishes recall with a single I.M. injection

Patients treated with VERSED I.M. had significantly less recall of memory cards (22/71) shown during the preanesthetic period than patients treated with hydroxyzine (70/79). Amnesia was greatest 30 to 60 minutes after administration. And when VERSED was given with scopolamine, the period of diminished recall extended to 90 minutes.

Compatible with other agents in the same syringe

VERSED can be mixed in the same syringe with other frequently used premedicants: morphine sulfate, meperidine, atropine sulfate or scopolamine.

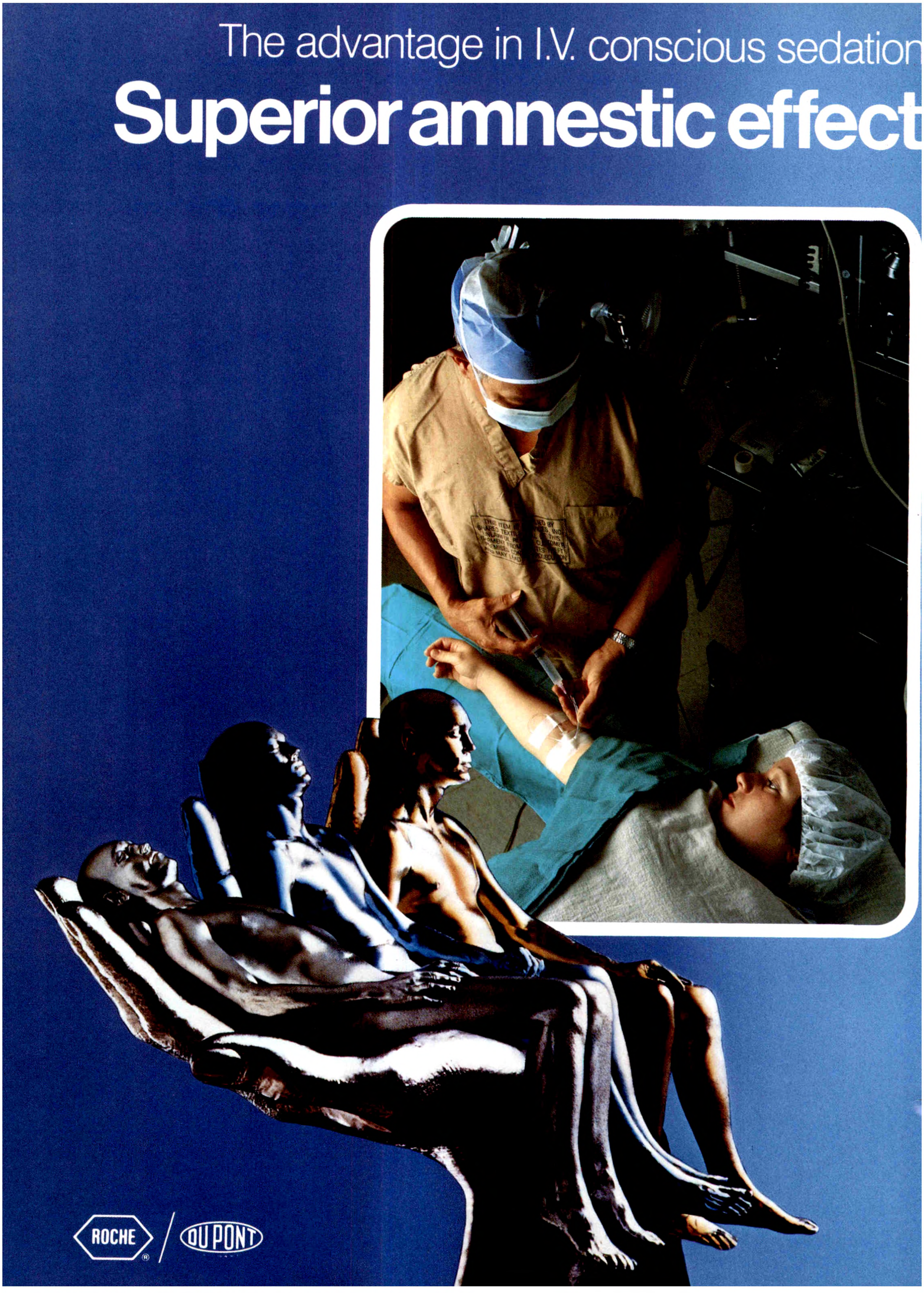
NEW

INJECTABLE

VERSED®

brand of
midazolam HCl Roche CIV

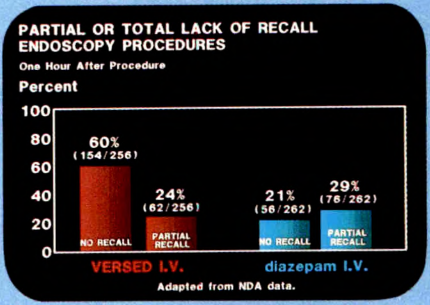
Please note Dosage and Administration Guidelines and see complete product information on last pages of this advertisement.


The advantage in I.V. conscious sedation
Superior amnestic effect
ROCHE
DUPONT

...less tissue irritation

Significantly less recall

In double-blind, multicenter studies, patients treated with VERSED had significantly less recall of endoscopic procedures than patients receiving diazepam. Of 256 VERSED patients, well over half—60%—had no recall of their procedures when questioned one hour later. By contrast, only 21% of 262 diazepam patients had a similar lack of recall.



Adapted from NDA data.

Use of a topical anesthetic for peroral procedures and narcotic premedication for bronchoscopies is recommended.

Less irritation

VERSED produced less pain or burning during I.V. administration than diazepam. VERSED also produced less postprocedural irritation: One week following I.V. administration, only 1.4% of 512 patients who received VERSED had tenderness of the vein compared with 3.0% of 503 patients who received diazepam (*P*=0.07).

Faster onset

In the majority of clinical studies, the time required to reach the end point of slurred speech was significantly shorter when patients received VERSED I.V. rather than diazepam I.V. For most procedures, VERSED induced sedation in mean times of 2.8 to 4.8 minutes, while diazepam required mean times of 2.6 to 9.0 minutes.

As a standard precaution, prior to the I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available and a person skilled in maintaining a patent airway and supporting ventilation should be present. Extra care should be observed in the elderly and debilitated, and in those with limited pulmonary reserve. Dosage of VERSED should be lowered by about 25% to 30% if narcotic premedication is used. Caution patients about driving or operating hazardous machinery after receiving VERSED.

NEW

INJECTABLE

VERSED®

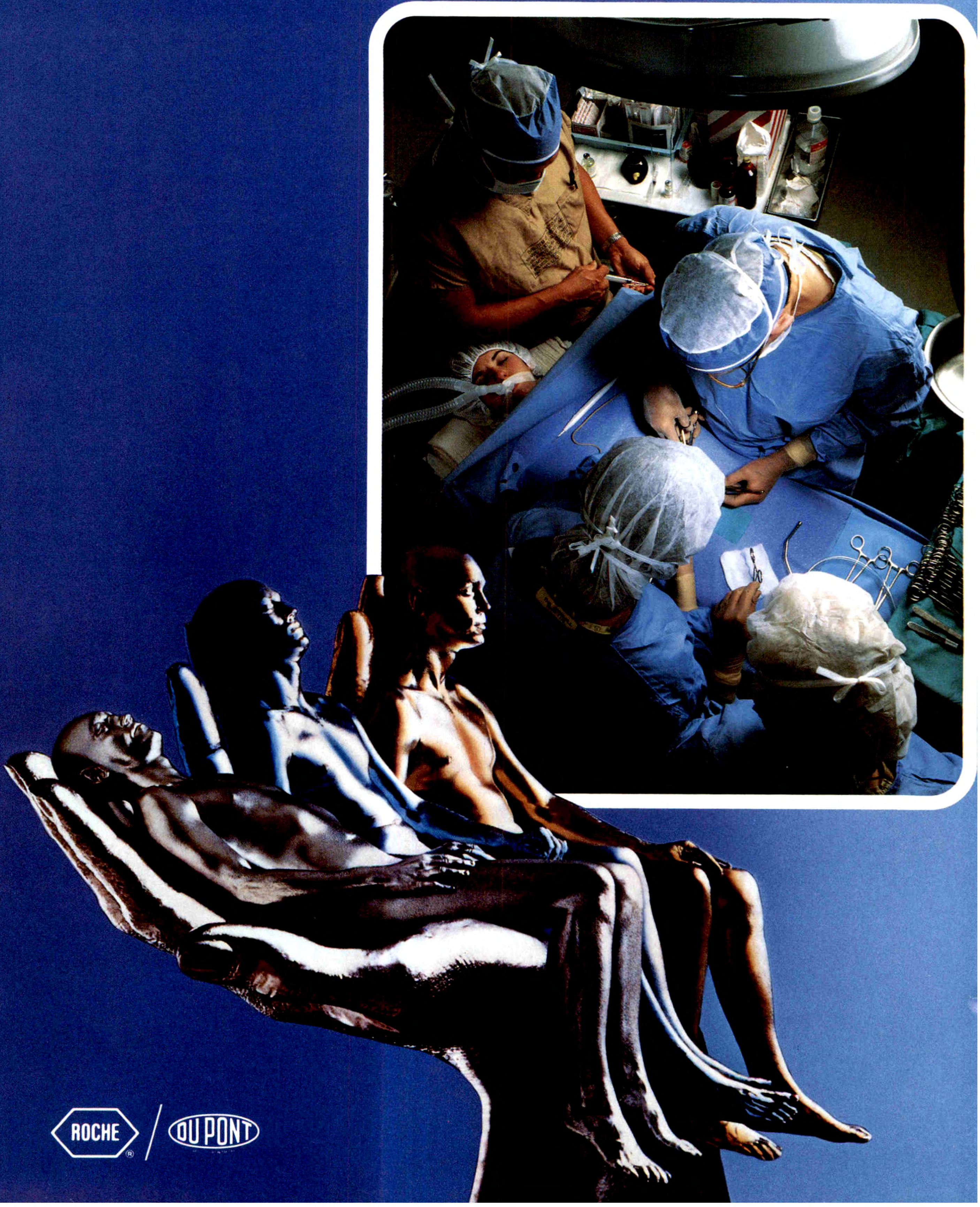
brand of midazolam HCl

Roche Ⓒ IV

Please note Dosage and Administration Guidelines and see complete product information on last pages of this advertisement.

The advantage in anesthetic induction and

Smooth induction...



ROCHE® / DU PONT

balanced anesthesia

smooth emergence

Smooth induction of anesthesia

Intravenous VERSED provides induction of general anesthesia, prior to administration of other anesthetic agents, as effectively as thiopental in properly premedicated patients. And it does so with significantly less apnea. Among 155 premedicated patients who received VERSED, 37% had apnea, compared to 54% of 137 premedicated patients given thiopental.

VERSED I.V. should be administered slowly, with the initial dose given over 20 to 30 seconds and titrated to desired effect. Avoid intra-arterial injection or extravasation. (See Warnings section of complete product information.) Dosages of VERSED should be lowered if sedative or narcotic premedication is used.

Minimal adverse hemodynamic effects

While the hemodynamic effects of VERSED I.V. do not differ significantly from those of thiopental, they are somewhat less pronounced. Standard resuscitative equipment should be available, however, and extra care observed in elderly or debilitated patients, and in patients with limited pulmonary reserve. VERSED should be administered as an induction agent only by a person trained in anesthesiology.

Valuable as a component of balanced anesthesia for short surgical procedures

VERSED not only works rapidly and safely, it's easily titrated during balanced anesthesia.

Compatible—ready to use

VERSED is compatible with 5% dextrose in water, normal saline and lactated Ringer's solution. No reconstitution or refrigeration is needed. VERSED is available in unit-dose and multidose vials and Tel-E-Ject® disposable syringes.

NEW

INJECTABLE

VERSED®

brand of

midazolam HCl

Roche CIV

Please note Dosage and Administration Guidelines and see complete product information on last pages of this advertisement.

Dosage and Administration Guidelines

Indication	Usual Adult Dose	Administration
Premedication	0.07-0.08 mg/kg Approx. 5 mg in the average adult.	I.M., deep in a large muscle mass, approx. one hour before surgery. May be mixed with morphine sulfate, meperidine, atropine or scopolamine.
I.V. Conscious Sedation	0.1-0.15 mg/kg is generally adequate, but up to 0.2 mg/kg may be given. Lower dosage by 25-30% when narcotic premedication is given. Patients over 60 require lower doses—reduce by 30%. Increments of 25% of initial dose to maintain desired level of sedation.	Slow I.V. administration into a large vein; titrate to desired sedative end point, *i.e., slurred speech*. Administer immediately before the procedure. Use of a topical anesthetic for peroral procedures and narcotic premedication for bronchoscopies is recommended. IMPORTANT: Start with the lowest dose of the range and titrate slowly.
Induction	**Premedicated Patients** Range: 0.15-0.35 mg/kg Average adult under 55: 0.25 mg/kg Over 55, ASA I or II: initial dose of 0.2 mg/kg ASA III or IV: 0.15 mg/kg **Unpremedicated Patients** Average adult under 55: 0.3-0.35 mg/kg initially, up to 0.6 mg/kg Over 55: initial dose of 0.3 mg/kg ASA III or IV: initial dose of 0.2-0.25 mg/kg Minimum dose of 0.15 mg/kg	Slow I.V. administration into a large vein. IMPORTANT: Start with the lowest dose of the range and titrate slowly. If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used.
As a component of balanced anesthesia for short surgical procedures	Approximately 25% of the induction dose should be given in response to signs of lightening of anesthesia and repeated as necessary.	

VERSED is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; however, they may be used in patients with open angle glaucoma only if they are receiving appropriate therapy.

Titrate to desired effect

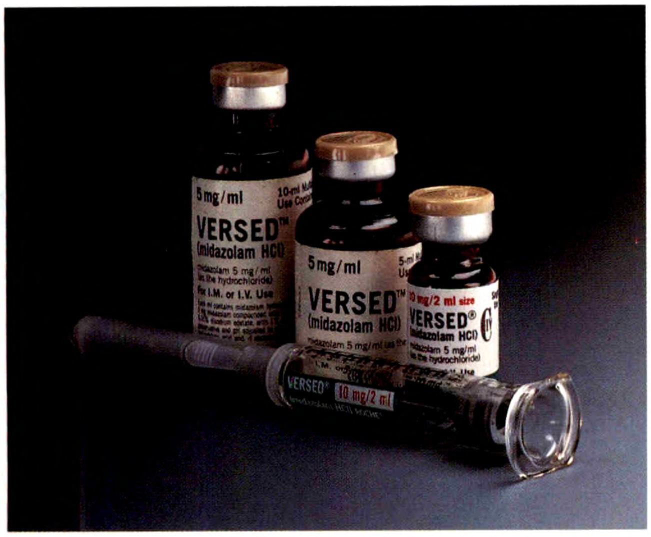
ROCHE / DUPONT

NEW

INJECTABLE

VERSED

brand of midazolam HCl Roche IV



VERSED® (brand of midazolam HCl/Roche) INJECTABLE Ⓒ

DESCRIPTION: VERSED (brand of midazolam hydrochloride/Roche) is a water-soluble benzodiazepine available as a sterile parenteral dosage form for intravenous or intramuscular injection. Each ml contains midazolam hydrochloride equivalent to 5 mg midazolam compounded with 0.8% sodium chloride and 0.01% disodium edetate, with 1% benzyl alcohol as preservative; the pH is adjusted to approximately 3 with hydrochloric acid and, if necessary, sodium hydroxide.

Chemically, midazolam is 8-chloro-6-(2-fluorophenyl)-1-methyl-*4H*-imidazo[1,5-a] [1,4]benzodiazepine. It is a white to light yellow crystalline compound, insoluble in water; the hydrochloride salt is soluble in aqueous solutions. Midazolam has a calculated molecular weight of 325.78.

CLINICAL PHARMACOLOGY: VERSED is a short-acting benzodiazepine central nervous system depressant.

The effects of VERSED on the CNS are dependent on the dose administered, the route of administration, and the presence or absence of other premedications. Onset time of sedative effects after IM administration was 15 minutes, with peak sedation occurring 30 to 60 minutes following injection. In one study, when tested the following day, 73% of the patients who received VERSED intramuscularly had no recall of memory cards shown 30 minutes following drug administration; 40% had no recall of the memory cards shown 60 minutes following drug administration.

Sedation after IV injection was achieved within 3 to 5 minutes; the time of onset is affected by total dose administered and the concurrent administration of narcotic premedication. Seventy-one percent of the patients in the endoscopy studies had no recall of introduction of the endoscope; 82% of the patients had no recall of withdrawal of the endoscope.

When VERSED is given intravenously as an anesthetic induction agent, induction of anesthesia occurs in approximately 1.5 minutes when narcotic premedication has been administered and in 2 to 2.5 minutes without narcotic premedication or with sedative premedication. Some impairment in a test of memory was noted in 90% of the patients studied.

VERSED, used as directed, does not delay awakening from general anesthesia. Gross tests of recovery after awakening (orientation, ability to stand and walk, suitability for discharge from the recovery room, return to baseline Trieger competency) usually indicate recovery within 2 hours but recovery may take up to 6 hours in some cases. When compared with patients who received thiopental, patients who received midazolam generally recovered at a slightly slower rate. Reaction time under stress (operating automobiles or other hazardous machinery) has not been studied. (See WARNINGS.)

The intravenous administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

In patients without intracranial lesions, induction with VERSED is associated with a moderate decrease in cerebrospinal fluid pressure (lumbar puncture measurements), similar to that seen following use of thiopental. Preliminary data in intracranial surgical patients with normal intracranial pressure but decreased compliance (subarachnoid screw measurements) show comparable elevations of intracranial pressure with VERSED and with thiopental during intubation.

Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with VERSED; patients with glaucoma have not been studied.

Usual intramuscular premedicating doses of VERSED do not depress the ventilatory response to carbon dioxide stimulation to a clinically significant extent. Induction doses of VERSED depress the ventilatory response to carbon dioxide stimulation for 15 minutes or more beyond the duration of ventilatory depression following administration of thiopental. Impairment of ventilatory response to carbon dioxide is more marked in patients with chronic obstructive pulmonary disease (COPD). Sedation with intravenous VERSED does not adversely affect the mechanics of respiration (resistance, static recoil, most lung volume measurements); total lung capacity and peak expiratory flow decrease significantly but static compliance and maximum expiratory flow at 50% of awake total lung capacity (Vmax) increase.

In cardiac hemodynamic studies, induction with VERSED was associated with a slight to moderate decrease in mean arterial pressure, cardiac output, stroke volume and systemic vascular resistance. Slow heart rates (less than 65/minute), particularly in patients taking propranolol for angina, tended to rise slightly; faster heart rates (*e.g.*, 85/minute) tended to slow slightly.

The following preliminary pharmacokinetic data for midazolam have been reported. In normal subjects and healthy patients intravenous midazolam exhibited an elimination half-life of 1.2 to 12.3 hours, a large volume of distribution (0.95 to 6.6 L/kg) and a plasma clearance of 0.15 to 0.77 L/hr/kg.

Following intravenous administration, less than 0.03% of the dose is excreted in the urine as intact midazolam. Midazolam is rapidly metabolized to 1-hydroxymethyl midazolam which is conjugated with subsequent excretion in the urine. Approximately 45% to 57% of the dose is excreted in the urine as the conjugate of 1-hydroxymethyl midazolam, the major metabolite of midazolam. The half-life of elimination of 1-hydroxymethyl midazolam is similar to the parent compound. The concentration of midazolam is 10- to 30-fold greater than that of 1-hydroxymethyl midazolam after single IV administration.

Clinical effects of VERSED do not directly correlate with the blood concentrations of midazolam.

In a small group of patients (n = 11) with congestive heart failure, there appeared to be a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam; however, the total body clearance of midazolam appeared to remain unchanged at a single 5-mg intravenous dose. There was no apparent change in the pharmacokinetic profile following the intravenous administration of 5 mg of midazolam to a small group of patients (n = 12) with hepatic dysfunction. There was a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution in a small group of patients (n = 15) with chronic renal failure.

In a small group (n = 12) of surgical patients, aged 49 to 60 years old, given 0.2 mg/kg midazolam intravenously, there appeared to be a small increase in the volume of distribution and elimination half-life with little change in total body clearance compared to an equal number of younger surgical patients (aged 18 to 30).

The mean absolute bioavailability of midazolam following intramuscular administration is greater than 90%. The mean time of maximum midazolam plasma concentrations following intramuscular dosing occurs within 45 minutes postadministration. Peak concentrations of midazolam as well as 1-hydroxymethyl midazolam after intramuscular administration are about one-half of those achieved after equivalent intravenous doses. The pharmacokinetic profile of elimination after intramuscularly administered midazolam is comparable to that observed following intravenous administration of the drug. Dose-linearity relationships have not been adequately defined.

Midazolam is approximately 97% plasma protein-bound in normal subjects and patients with renal failure. In animals, midazolam has been shown to cross the blood-brain barrier. In animals and in humans, midazolam has been shown to cross the placenta and enter into fetal circulation. It is not known whether midazolam is excreted in human milk.

INDICATIONS: Injectable VERSED is indicated—

- intramuscularly for preoperative sedation (induction of sleepiness or drowsiness and relief of apprehension) and to impair memory of peri-operative events;
- intravenously as an agent for conscious sedation prior to short diagnostic or endoscopic procedures, such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography and cardiac catheterization, either alone or with a narcotic;
- intravenously for induction of general anesthesia, before administration of other anesthetic agents. With the use of narcotic premedication, induction of anesthesia can be attained within a relatively narrow dose range and in a short period of time. Intravenous VERSED can also be used as a component of intravenous supplementation of nitrous oxide and oxygen (balanced anesthesia) *for short surgical procedures*; longer procedures have not been studied.

When used intravenously, VERSED is associated with a high incidence of partial or complete impairment of recall for the next several hours. (See CLINICAL PHARMACOLOGY.)

CONTRAINDICATIONS: Injectable VERSED is contraindicated in patients with a known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma only if they are receiving appropriate therapy. (See CLINICAL PHARMACOLOGY.)

WARNINGS: PRIOR TO THE INTRAVENOUS ADMINISTRATION OF VERSED IN ANY DOSE, THE IMMEDIATE AVAILABILITY OF OXYGEN AND RESUSCITATIVE EQUIPMENT FOR THE MAINTENANCE OF A PATENT AIRWAY AND SUPPORT OF VENTILATION SHOULD BE ENSURED. Because intravenous VERSED depresses respiration (see CLINICAL PHARMACOLOGY) and because opioid agonists and other sedatives can add to this depression, VERSED should be administered as an induction agent only by a person trained in general anesthesia and should be used in conscious sedation only when a person skilled in maintaining a patent airway and supporting ventilation is present.

Injectable VERSED should not be administered to patients in shock or coma, or in acute alcohol intoxication with depression of vital signs.

The hazards of intra-arterial injection of VERSED solutions in humans are unknown; therefore, extreme precautions against unintended intra-arterial injection should be taken. Extravasation should also be avoided.

Higher risk surgical patients or debilitated patients require lower dosages for induction of anesthesia, whether premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure have a 1.5- to 2-fold increase in elimination half-life, total body clearance and volume of distribution of midazolam. Patients with congestive heart failure have a 2- to 3-fold increase in the elimination half-life and volume of distribution of midazolam. Patients over the age of 55 years require lower dosages for induction of anesthesia, whether premedicated or not. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduced initial dosage of VERSED is recommended and the possibility of profound and/or prolonged effect should be considered.

Concomitant use of barbiturates, alcohol or other central nervous system depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with a narcotic.

The decision as to when patients who have received injectable VERSED, particularly on an outpatient basis, may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle, must be individualized. Gross tests of recovery from the effects of VERSED (see CLINICAL PHARMACOLOGY) cannot be relied upon alone to predict reaction time under stress. This drug is never used alone during anesthesia and the contribution of other peri-operative drugs and events can vary. It is recommended that no patient operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia and surgery, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepine drugs (diazepam and chlordiazepoxide) has been suggested in several studies. If this drug is used during pregnancy, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS: *General:* Because an increase in cough reflex and laryngospasm may occur with peroral endoscopic procedures, the use of a topical anesthetic agent and the availability of necessary countermeasures are recommended. The use of narcotic premedication is recommended for bronchoscopies. Intravenous doses of VERSED should be decreased by 25% to 30% for elderly and debilitated patients. (See WARNINGS and DOSAGE AND ADMINISTRATION.) These patients will also probably take longer to recover completely after VERSED administration for the induction of anesthesia.

VERSED does not protect against the increase in intracranial pressure or circulatory effects noted following administration of succinylcholine.

VERSED does not protect against the increase in intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: To assure safe and effective use of benzodiazepines, the following information and instructions should be communicated to the patient when appropriate:

1. Inform your physician about any alcohol consumption and medicine you are now taking, including drugs you buy without a prescription. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol during benzodiazepine treatment.
2. Inform your physician if you are pregnant or are planning to become pregnant.
3. Inform your physician if you are nursing.

Drug interactions: The hypnotic effect of intravenous VERSED is accentuated by premedication, particularly narcotics (*e.g.*, morphine, meperidine and fentanyl) and also secobarbital and Innovar (fentanyl and droperidol). Consequently, the dosage of VERSED should be adjusted according to the type and amount of premedication administered. (See DOSAGE AND ADMINISTRATION.)

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of intramuscular VERSED for premedication.

The use of VERSED as an induction agent may result in a reduction of the inhalation anesthetic requirement during maintenance of anesthesia. (See CLINICAL PHARMACOLOGY.)

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium and does not protect against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine.

No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with results obtained in clinical laboratory tests.

Carcinogenesis, mutagenesis, impairment of fertility:
Carcinogenesis: Midazolam maleate was administered with diet in mice and rats for two years at dosages of 1, 9 and 80 mg/kg/day. In female mice in the highest dose group there was a marked increase in the incidence of hepatic tumors. In high dose male rats there was a small but statistically significant increase in benign thyroid follicular cell tumors. Dosages of 9 mg/kg/day of midazolam maleate (25 times a human dose of 0.35 mg/kg) do not increase the incidence of tumors. The pathogenesis of induction of these tumors is not known. These tumors were found after chronic administration, whereas human use will ordinarily be of single or several doses.
Mutagenesis: Midazolam did not have mutagenic activity in *Salmonella typhimurium* (5 bacterial strains), Chinese hamster lung cells (V79), human lymphocytes, or in the micronucleus test in mice.
Impairment of fertility: A reproduction study in male and female rats did not show any impairment of fertility at dosages up to 10 times the human IV dose of 0.35 mg/kg.
Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section.
Segment II teratology studies, performed with midazolam maleate injectable in rabbits and rats at 5 and 10 times the human dose of 0.35 mg/kg, did not show evidence of teratogenicity.
Nonteratogenic effects: Studies in rats showed no adverse effects on reproductive parameters during gestation and lactation. Dosages tested were approximately 10 times the human dose of 0.35 mg/kg.
Labor and delivery: In humans, measurable levels of midazolam were found in maternal venous serum, umbilical venous and arterial serum and amniotic fluid, indicating placental transfer of the drug. Following intramuscular administration of 0.05 mg/kg of midazolam, both the venous and the umbilical arterial serum concentrations were lower than maternal concentrations.
The use of injectable VERSED in obstetrics has not been evaluated in clinical studies. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.
Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.
Pediatric use: Safety and effectiveness of VERSED in children below the age of 18 have not been established.
ADVERSE REACTIONS: Fluctuations in vital signs were the most frequently seen findings following parenteral administration of VERSED and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate. These are common occurrences during anesthesia and surgery and are affected by the lightening or deepening of anesthesia, instrumentation, intubation and use of concomitant drugs.
In the conscious sedation studies, hypotension occurred more frequently after IV administration of VERSED in patients concurrently premedicated with meperidine. It should especially be noted that VERSED does not modify the circulatory effects of neuromuscular blocking agents or the tachycardia and blood pressure rises seen during endotracheal intubation under light general anesthesia. During the clinical investigations, three cases (0.2%) of transient fall in blood pressure greater than 50% were reported during the induction phase.
The following adverse reactions were reported after intramuscular administration:

headache (1.3%)	*Local effects at IM injection site* pain (3.7%) induration (0.5%) redness (0.5%) muscle stiffness (0.3%)

The following adverse reactions were reported subsequent to intravenous administration:

hiccoughs (3.9%)	*Local effects at the IV site*
nausea (2.8%)	tenderness (5.6%)
vomiting (2.6%)	pain during injection (5.0%)
coughing (1.3%)	redness (2.6%)
"oversedation" (1.6%)	induration (1.7%)
headache (1.5%)	phlebitis (0.4%)
drowsiness (1.2%)	

Other adverse experiences, observed mainly following IV injection and occurring at an incidence of less than 1.0%, are as follows:
Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea.
Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm.
Gastrointestinal: Acid taste, excessive salivation, retching.
CNS/Neuromuscular: Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, agitation, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, tonic/clonic movements, muscle tremor, involuntary movements, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paresthesia.
Special Sense: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness.
Integumentary: Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus.
Miscellaneous: Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.
DRUG ABUSE AND DEPENDENCE: Midazolam is subject to Schedule IV control under the Controlled Substances Act of 1970.
Midazolam was actively self-administered in primate models used to assess the positive reinforcing effects of psychoactive drugs.
Midazolam produced physical dependence of a mild to moderate intensity in cynomolgus monkeys after 5 to 10 weeks of administration. Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.
OVERDOSAGE: There have been no reports of injectable VERSED overdosage. The manifestations of VERSED overdosage are expected to be similar to those observed with other benzodiazepines and include sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma and untoward effects on vital signs. No evidence of specific organ toxicity from VERSED overdosage would be expected.
Treatment of overdosage: Treatment of injectable VERSED overdosage is the same as that followed for overdosage with other benzodiazepines. Respiration, pulse rate and blood pressure should be monitored and general supportive measures should be employed. Attention should be given to the maintenance of a patent airway and support of ventilation. An intravenous infusion should be started. Should hypotension develop, treatment may include intravenous fluid therapy, repositioning, judicious use of vasopressors appropriate to the clinical situation, if indicated, and other appropriate countermeasures. There is no information as to whether peritoneal dialysis, forced diuresis or hemodialysis are of any value in the treatment of midazolam overdosage.
DOSAGE AND ADMINISTRATION: Dosage should be individualized. In general, lower doses are required in elderly or debilitated patients. The dosage of intravenous VERSED administered should be adjusted according to the type and amount of premedication used. When intravenous use is indicated, oxygen, resuscitative equipment and personnel resources for the maintenance of a patent airway should be immediately available. (See WARNINGS.)
Injectable VERSED may be mixed in the same syringe with the following frequently used premedications: morphine sulfate, meperidine, atropine sulfate or scopolamine. Injectable VERSED is compatible with 5% dextrose in water, 0.9% sodium chloride and lactated Ringer's solution.
For *intramuscular* use, VERSED should be injected deep in a large muscle mass. *Intravenous* VERSED for conscious sedation should be administered slowly; rapid injection may cause respiratory depression or apnea requiring assisted or controlled ventilation. For induction of general anesthesia, the initial dose should be administered over 20 to 30 seconds for optimum effect. Extreme care should be taken to avoid intra-arterial injection or extravasation (see WARNINGS).

	USUAL ADULT DOSE
INTRAMUSCULARLY For preoperative sedation (induction of sleepiness or drowsiness and relief of apprehension) and to impair memory of peri-operative events.	For premedication the recommended dos VERSED is 0.07 to 0.08 mg/kg IM (appr mately 5 mg IM for an average adult) appr mately one hour before surgery. Onset is wi 15 minutes, peaking at 30 to 60 minutes. It be administered concomitantly with atropine fate or scopolamine hydrochloride and redu doses of narcotics.
INTRAVENOUSLY *Endoscopic or Cardiovascular Procedures* For conscious sedation, VERSED can be used either alone or together with a narcotic immediately before the procedure with supplemental doses of VERSED to maintain the desired level of sedation throughout the procedure. For peroral procedures, the use of an appropriate topical anesthetic is recommended. For bronchoscopic procedures, the use of narcotic premedication is recommended.	Titrate dosage to desired sedative end point, slurring of speech, with slow administrat immediately prior to the procedure. Generally to 0.15 mg/kg is adequate, but up to 0.2 mg may be given, particularly when concomit narcotics are omitted. Doses in excess of mg/kg may result in increased risk of respirat depression or drowsiness in elderly or debilita patients. Additional maintenance doses may given in increments of 25% of the initial dos maintain the desired level of sedation. Narcotic premedication results in less variab in patient response. Dosage should be lowe by about 25% to 30% if narcotic premedicatio used. Patients 60 years or older may requ lower doses (by about 30%) than youn patients.
Induction of Anesthesia For induction of general anesthesia, before administration of other anesthetic agents.	Individual response to the drug is variable, ticularly when a narcotic premedication is used. The dosage should be titrated to desired effect according to the patient's age clinical status. *Unpremedicated Patients* In the absence of premedication, an aver adult under the age of 55 years will usu require an initial dose of 0.3 to 0.35 mg/kg induction, administered over 20 to 30 seco and allowing 2 minutes for effect. If neede complete induction, increments of appro mately 25% of the patient's initial dose may used; induction may instead be completed volatile liquid inhalational anesthetics. In res ant cases, up to 0.6 mg/kg total dose may used for induction, but such larger doses r prolong recovery. Unpremedicated patients over the age of 55 ye usually require less VERSED for induction; an tial dose of 0.3 mg/kg is recommended. Un medicated patients with severe systemic dise or other debilitation usually require less VERS for induction. An initial dose of 0.2 to 0.25 mg will usually suffice; in some cases, as little 0.15 mg/kg may suffice. *Premedicated Patients* When the patient has received sedative or cotic premedication, particularly narcotic medication, the range of recommended dose 0.15 to 0.35 mg/kg. In average adults below the age of 55 year dose of 0.25 mg/kg, administered over 20 t seconds and allowing 2 minutes for effect, usually suffice. The initial dose of 0.2 mg/kg is recommende good risk (ASA I and II) surgical patients over age of 55 years. In some patients with severe systemic diseas debilitation, as little as 0.15 mg/kg may suffic Narcotic premedication frequently used du clinical trials included fentanyl (1.5 to 2 µg/kg administered 5 minutes before induction), m phine (dosage individualized, up to 0.15 mg IM), meperidine (dosage individualized, up mg/kg IM) and Innovar (0.02 ml/kg IM). Seda premedications were hydroxyzine pamoate (mg orally) and sodium secobarbital (200 orally). Except for intravenous fentanyl, admi tered 5 minutes before induction, all other medications should be administe approximately one hour prior to the time an pated for VERSED induction.
Injectable VERSED can also be used during maintenance of anesthesia, *for short surgical procedures*, as a component of balanced anesthesia. Effective narcotic premedication is especially recommended in such cases. Long surgical procedures have not been studied.	Incremental injections of approximately 25 the induction dose should be given in respons signs of lightening of anesthesia and repeate necessary.

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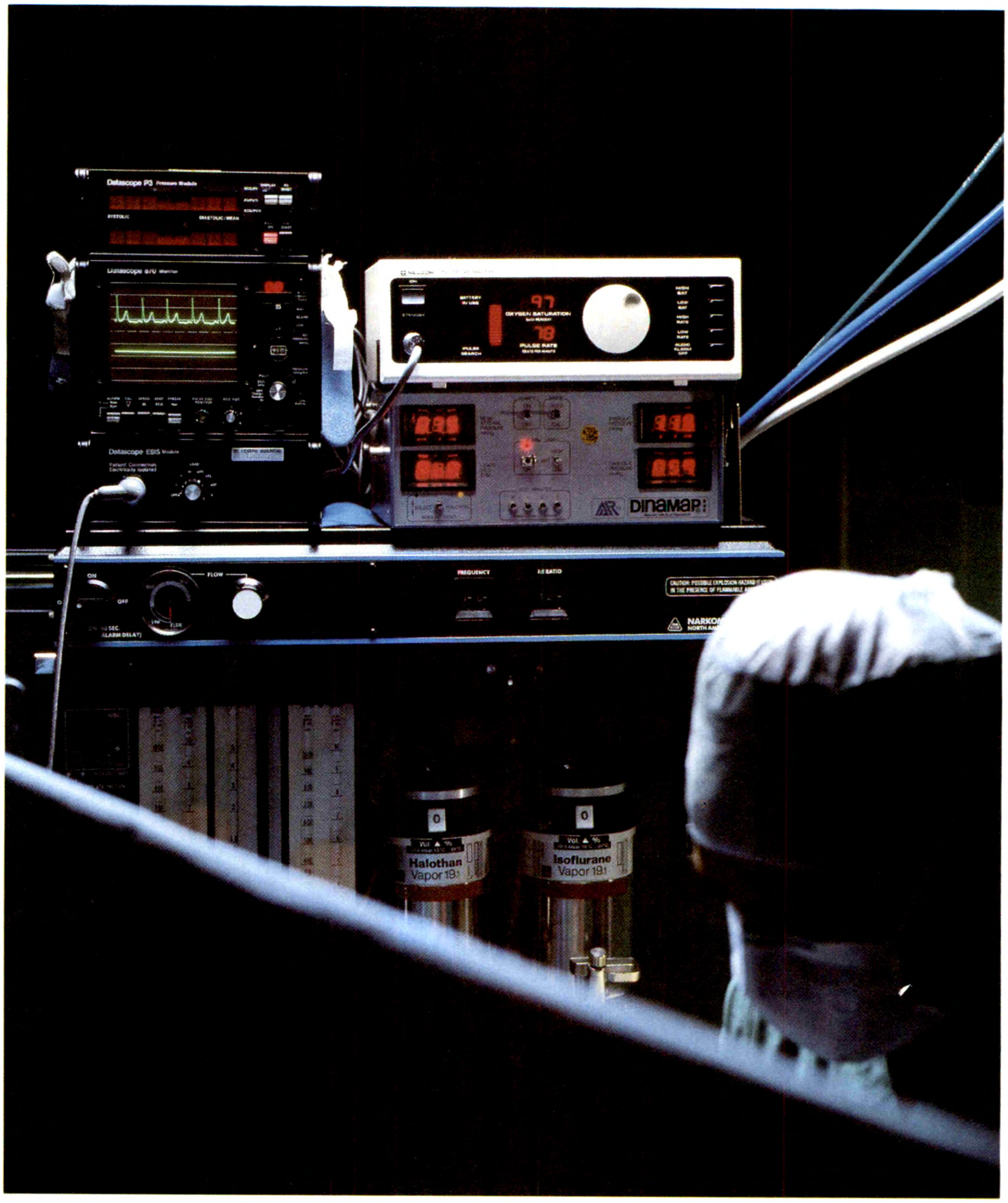
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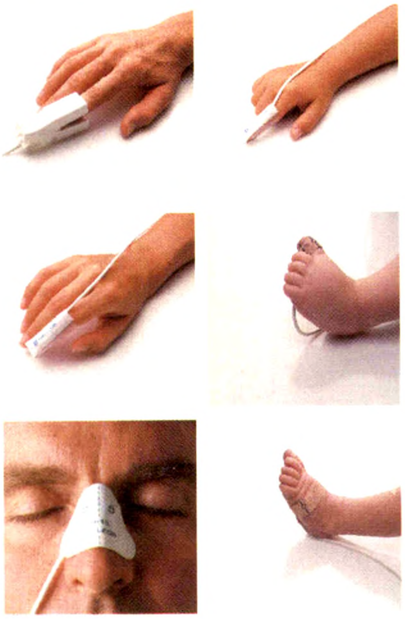

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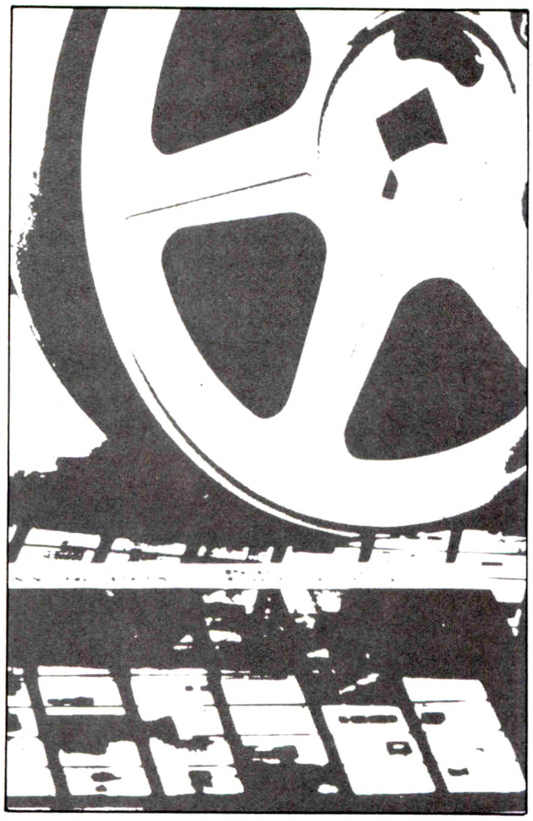

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Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

CAUTION: Federal law prohibits dispensing without prescription.

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Anesthesia and Analgesia

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ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

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THE SUFENTA® REPORT

A PRACTICAL ANESTHESIA UPDATE

VOL. 1, NO. 1 JANSSEN PHARMACEUTICA INC. WINTER 1986

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SAN FRANCISCO: Low doses of SUFENTA® (sufentanil citrate) Injection Ⓒ, given prior to thiopental as an adjunct to induction, improved hemodynamic stability and reduced barbiturate requirements, according to a study presented here at the 1985 Annual Meeting of the A.S.A. In a group of 30 adult patients who underwent surgery of 25 min. to 8.5 hr. duration, thiopental was used for induction, either alone or combined with SUFENTA. SUFENTA (0.5 or 1.0 μg/kg) reduced thiopental requirements by 50% to 68%, respectively, and the hemodynamic response to laryngoscopy and intubation was attenuated, as measured by systolic pressure, heart rate and rate-pressure product. Bradycardia, truncal rigidity and recall were not observed.

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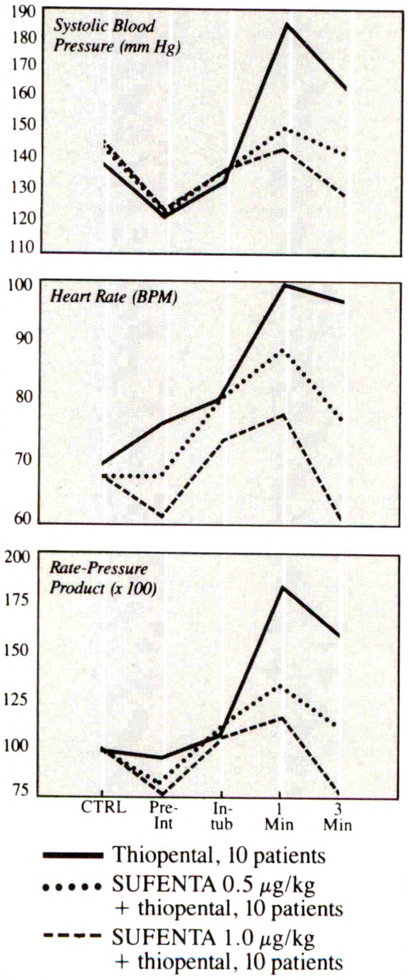

(Abstracted from Brizgys, Morales and Owens, *Anesthesiology* 1985; 63:A377)

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Clinical experience with SUFENTA in general surgery revealed that *total dosage requirements averaged about 1 μg/kg/hour or less,* in surgery up to 8 hours.

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Adult Dosage Recommendations: A Summary

Please see full Prescribing Information, including dosage, on next page.

	General Surgical Procedures	Major Surgical Procedures
Expected Duration	1 to 2 hours	2 to 8 hours
Types of Procedures	Total vaginal hysterectomy, gall bladder surgery, bilateral inguinal hernia repair, open reduction of fractures	Major orthopedic surgery, carotid endarterectomy, nephrectomy, major abdominal surgery (e.g., colectomy)
Recommended Induction Dose	1 to 1.5 μg/kg (1.4 to 2.1 ml for a 70 kg patient), administered with N_2O/O_2, endotracheal intubation and mechanical ventilation	1 to 5 μg/kg (1.4 to 7 ml for a 70 kg patient), administered with N_2O/O_2, endotracheal intubation and mechanical ventilation
Recommended Maintenance Dose	10 to 25 μg (0.2 to 0.5 ml) based upon changes in clinical signs and patient's response to initial dose	10 to 25 μg (0.2 to 0.5 ml) based upon changes in clinical signs and patient's response to initial dose
Total Dosage	For cases lasting 2 hours, would not be expected to exceed 2 μg/kg (2.8 ml for a 70 kg patient) when used with N_2O/O_2	For cases lasting 8 hours, would not be expected to exceed 8 μg/kg (11.2 ml for a 70 kg patient) when used with N_2O/O_2

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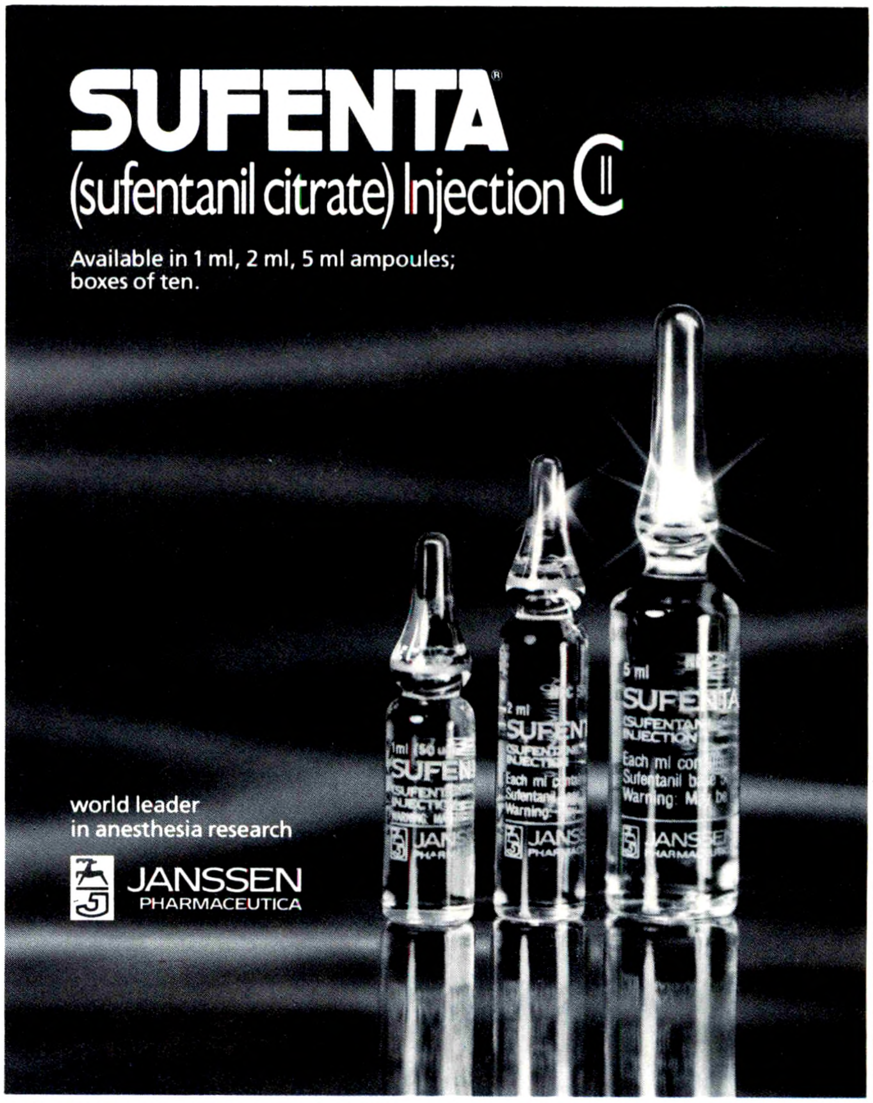

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DESCRIPTION: SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[-4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

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CLINICAL PHARMACOLOGY: SUFENTA is an opioid analgesic. When used in balanced general anesthesia, SUFENTA has been reported to be as much as 10 times as potent as fentanyl. When administered as a primary anesthetic agent with 100% oxygen, SUFENTA is approximately 5 to 7 times as potent as fentanyl. (See dosage chart for more complete information on the use of SUFENTA.) At doses of up to 8 µg/kg, SUFENTA provides profound analgesia; at doses ≥8 µg/kg, SUFENTA produces a deep level of anesthesia. SUFENTA produces a dose related attenuation of catecholamine release, particularly norepinephrine.

The pharmacokinetics of SUFENTA can be described as a three-compartment model, with a distribution time of 1.4 minutes, redistribution of 17.1 minutes and an elimination half-life of 164 minutes. The liver and small intestine are the major sites of biotransformation. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug. Plasma protein binding of SUFENTA is approximately 92.5%.

SUFENTA has an immediate onset of action, with relatively limited accumulation. Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with equipotent dosages of fentanyl. At dosages of SUFENTA of 1-2 µg/kg, recovery times are comparable to those observed with fentanyl; at dosages of >2-6 µg/kg, recovery times are comparable to enflurane, isoflurane and fentanyl. Within the anesthetic dosage range of 8-30 µg/kg of SUFENTA, recovery times are more rapid compared to equipotent fentanyl dosages.

At dosages of ≥8 µg/kg, SUFENTA produces hypnosis and anesthesia without the use of additional anesthetic agents. A deep level of anesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to 25 µg/kg attenuate the sympathetic response to surgical stress. The catecholamine response, particularly norepinephrine, is further attenuated at doses of SUFENTA of 25-30 µg/kg, with hemodynamic stability and preservation of favorable myocardial oxygen balance.

The vagolytic effects of pancuronium may produce a dose dependent elevation in heart rate during SUFENTA-oxygen anesthesia. The vagolytic effect of pancuronium may be reduced in patients administered nitrous oxide with SUFENTA. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent may be used to maintain a stable lower heart rate and blood pressure during SUFENTA-oxygen anesthesia.

Preliminary data suggest that in patients administered high doses of SUFENTA, initial dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane.

Bradycardia is infrequently seen in patients administered SUFENTA-oxygen anesthesia. The use of nitrous oxide with high doses of SUFENTA may decrease mean arterial pressure, heart rate and cardiac output.

Assays of histamine in patients administered SUFENTA have shown no elevation in plasma histamine levels and no indication of histamine release.

SUFENTA at 20 µg/kg has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anesthesia supplementation in one study of patients undergoing craniotomy. During carotid endarterectomy, SUFENTA-nitrous oxide/oxygen produced reductions in cerebral blood flow comparable to those of enflurane-nitrous oxide/oxygen. During cardiovascular surgery, SUFENTA-oxygen produced EEG patterns similar to fentanyl-oxygen; these EEG changes were judged to be compatible with adequate general anesthesia.

The intraoperative use of SUFENTA at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. The incidence of postoperative hypertension, need for vasoactive agents and requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of SUFENTA as compared to patients given inhalation agents.

Skeletal muscle rigidity is related to the dose and speed of administration of SUFENTA. This muscular rigidity may occur unless preventative measures are taken (see Warnings).

Decreased respiratory drive and increased airway resistance occur with SUFENTA. The duration and degree of respiratory depression are dose related when SUFENTA is used at sub-anesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced.

INDICATIONS AND USAGE: SUFENTA (sufentanil citrate)is indicated:

as an analgesic adjunct in the maintenance of balanced general anesthesia.

as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

SEE DOSAGE CHART FOR MORE COMPLETE INFORMATION ON THE USE OF SUFENTA.

CONTRAINDICATIONS: SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is dose related. Administration of SUFENTA may produce muscular rigidity with a more rapid onset than that seen with fentanyl. SUFENTA may produce muscular rigidity that involves the skeletal muscles of the neck and extremities. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of consciousness when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg).

The neuromuscular blocking agent should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: General: The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.

Vital signs should be monitored routinely.

Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY).

The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent.

High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO_2 stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to discharging the patient from the recovery area.

Interaction with Other Central Nervous System Depressants: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when SUFENTA is administered to patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced.

Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compro-mised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

Pregnancy Category C: SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits.

There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

Animal Toxicology: The intravenous LD_{50} of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

ADVERSE REACTIONS: The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%).

Other adverse reactions with a reported incidence of less than 1% were:

Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching, erythema
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

DRUG ABUSE AND DEPENDENCE: SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous LD_{50} of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for LD_{50}s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION: The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

See dosage range chart for the use of SUFENTA by intravenous injection 1) in doses of up to 8 µg/kg as an analgesic adjunct to general anesthesia, and 2) in doses ≥8 µg/kg as a primary anesthetic agent for induction and maintenance of anesthesia with 100% oxygen.

Usage in Children: For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 µg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of up to 25-50 µg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.

Premedication: The selection of preanesthetic medications should be based upon the needs of the individual patient.

Neuromuscular Blocking Agents: The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

ADULT DOSAGE RANGE CHART

TOTAL DOSAGE	MAINTENANCE DOSAGE
ADMINISTRATION WITH NITROUS OXIDE/OXYGEN FOR SURGICAL PROCEDURES LASTING UP TO EIGHT HOURS:	
• TOTAL DOSAGE REQUIREMENTS OF 1µG/KG/HR OR LESS ARE RECOMMENDED	
1-2 µg/kg: Expected duration of anesthesia 1-2 hours. Approximately 75% or more of total SUFENTA dosage may be administered prior to intubation. Administered with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.	**10-25 µg (0.2-0.5 ml):** as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to remaining operative time anticipated.
2-8 µg/kg: Expected duration of anesthesia 2-8 hours. Approximately 50 to 75% of total SUFENTA dosage may be administered prior to intubation. Administered with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures. At dosages in this range, SUFENTA has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli, provide hemodynamic stability, and provide relatively rapid recovery.	**10-50 µg (0.2-1 ml):** as determined by changes in vital signs that indicate stress or lightening of analgesia. Supplemental dosages should be individualized, and adjusted to the remaining operative time anticipated.
ADMINISTRATION WITH 100% OXYGEN	
8-30 µg/kg: (anesthetic doses) administered with 100% oxygen and a muscle relaxant. SUFENTA has been found to produce sleep at dosages ≥8 µg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. At dosages in this range of up to 25 µg/kg, catecholamine release is attenuated. Dosages of 25-30 µg/kg have been shown to block sympathetic responses including catecholamine release. High doses are indicated in patients undergoing major surgical procedures, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance. Postoperative mechanical ventilation and observation are essential at these dosages due to extended postoperative respiratory depression.	**25-50 µg/kg (0.5-1 ml):** as determined by changes in vital signs that indicate stress and lightening of anesthesia.

In patients administered high (anesthetic) doses of SUFENTA, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

For purposes of administering small volumes of SUFENTA accurately, the use of a tuberculin syringe or equivalent is recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

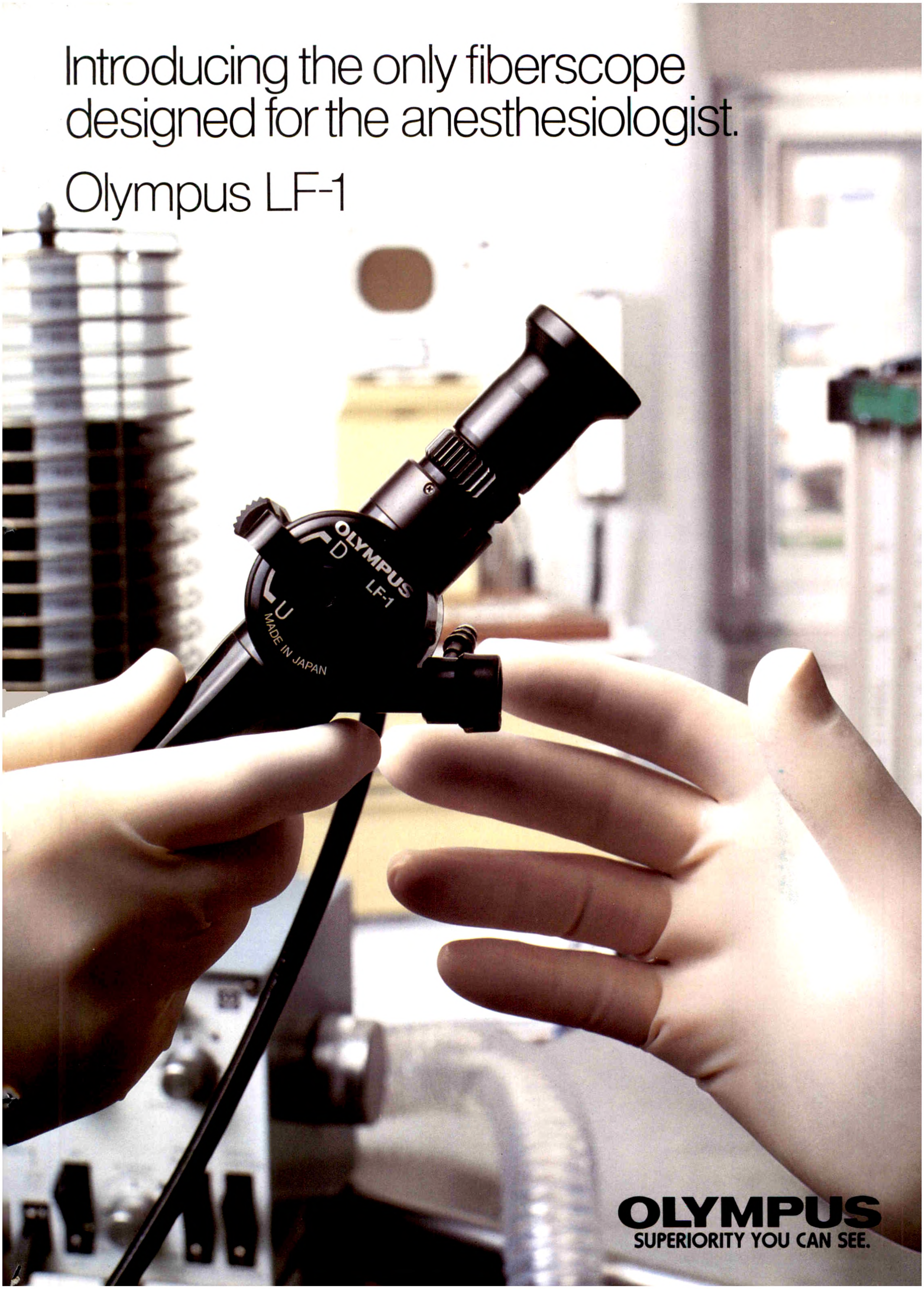
HOW SUPPLIED: SUFENTA (sufentanil citrate) Injection for intravenous use is available as:

NDC 50458-050-01	50 µg/ml, 1 ml ampoules in packages of 10
NDC 50458-050-02	50 µg/ml, 2 ml ampoules in packages of 10
NDC 50458-050-05	50 µg/ml, 5 ml ampoules in packages of 10

Protect from light.
Store at room temperature.

JANSSEN
PHARMACEUTICA
Janssen Pharmaceutica Inc.
Piscataway, NJ 08854

U.S Patent No. 3,998,834
7618503-M
May 1984, January 1986



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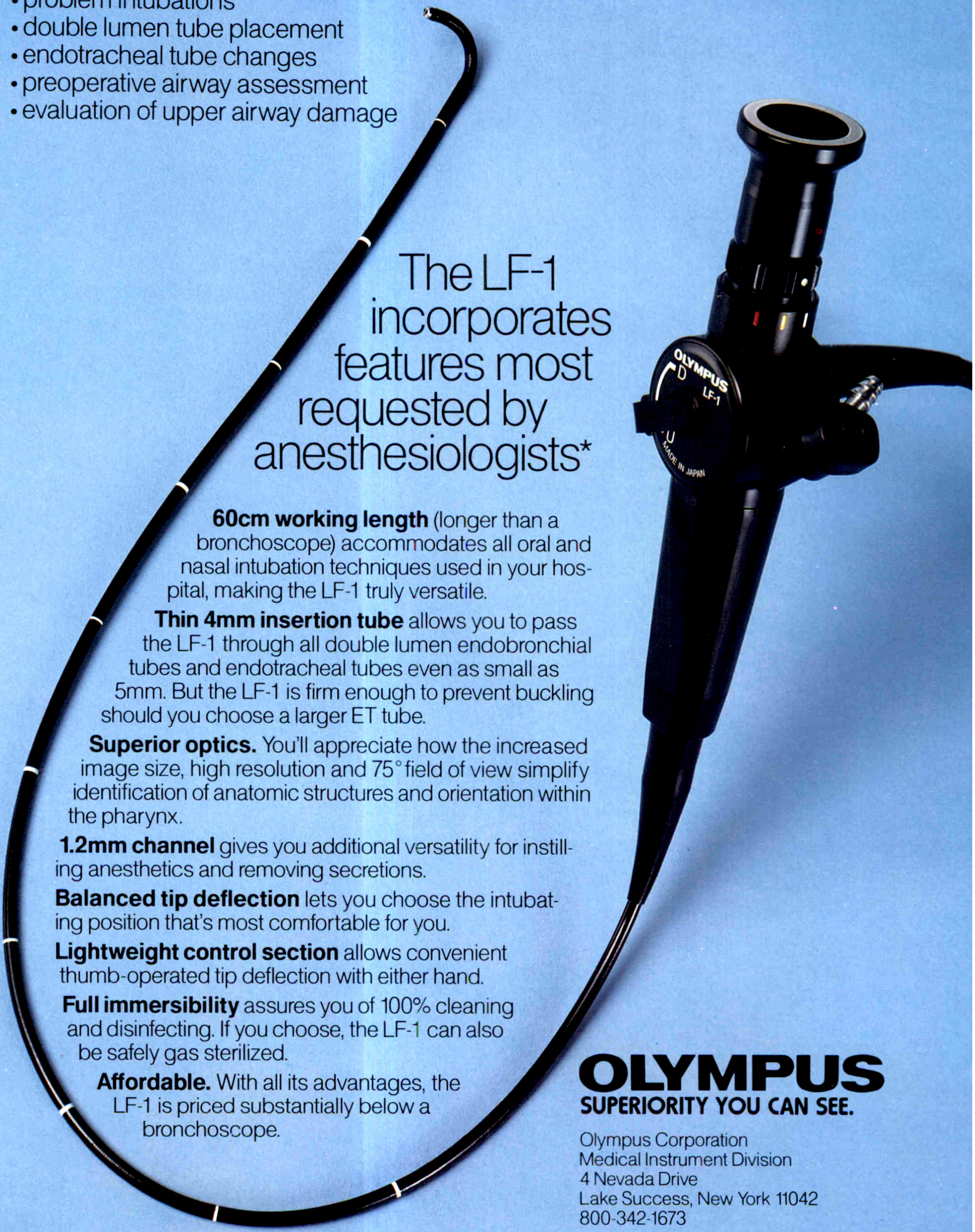

The LF-1 incorporates features most requested by anesthesiologists*

60cm working length (longer than a bronchoscope) accommodates all oral and nasal intubation techniques used in your hospital, making the LF-1 truly versatile.

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INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

1986 Awards

The Board of Trustees of the IARS is pleased to advise that four Awards were granted and announced at the March 1986 meeting in Las Vegas, as follows:

Zeljko J. Bosnjak, PhD, Medical College of Wisconsin, Milwaukee, WI:
"Effects of Chronic Administration of Calcium Antagonists"
John F. Butterworth IV, MD, Bowman Gray School of Medicine, Winston-Salem, NC:
"Brain Cellular Mechanisms of Increased Anesthetic Susceptibility with Aging"
Philippe R. Housmans, MD, PhD, Mayo Foundation, Rochester, MN:
"Influence of Halothane on Intracellular Calcium Handling in Mammalian Cardiac Muscle"
Vladimir Nigrovic, MD, Medical College of Ohio, Toledo, OH:
"Adverse Reactions and Metabolism of Atracurium"

1987 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

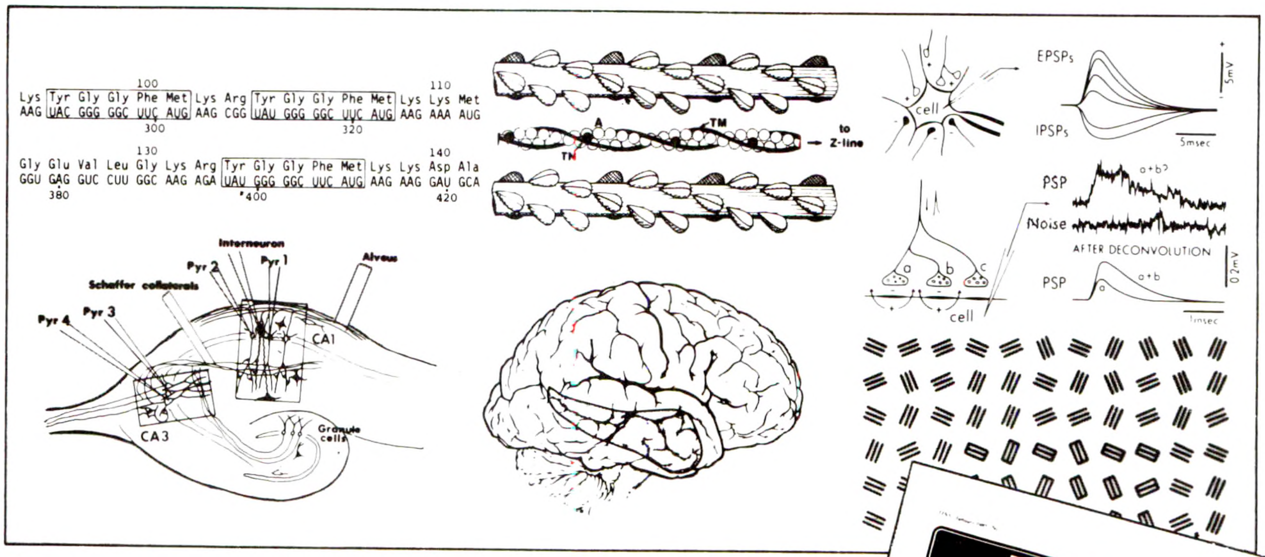
Applications for up to $25,000 are invited for the 1987 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education, or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office no later than December 15, 1986.
- The official application for the Award must be used. This form, as well as the guidelines for applicants, is available on request to:

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, OH 44122
Telephone: (216) 295-1124

The 1987 Award(s) will be announced at the Annual Scientific Meeting (61st Congress) of the International Anesthesia Research Society to be held at the Buena Vista Palace, Lake Buena Vista (Orlando), Florida, March 14-18, 1987.

Trends in NeuroSciences


100
110
Lys Tyr Gly Gly Phe Met Lys Arg Tyr Gly Gly Phe Met Lys Lys Met
AAG UAC GGG GGC UUC AUG AAG CGG UAU GGG GGC UUC AUG AAG AAA AUG
300
320
130
140
Gly Glu Val Leu Gly Lys Arg Tyr Gly Gly Phe Met Lys Lys Asp Ala
GGU GAG GUC CUU GGC AAG AGA UAU GGG GGC UUC AUG AAG AAG GAU GCA
380
400
420
A
TM
TM
to Z-line
cell
EPSPs
IPSPs
5mV
5msec
PSP
a+b?
Noise
AFTER DECONVOLUTION
0.2mV
PSP
a+b
a
a
b
c
cell
1msec
Interneuron
Pyr 2
Pyr 1
Alveus
Schaffer collaterals
Pyr 4
Pyr 3
CA1
CA3
Granule cells

From genes to behaviour –the central connection

This is probably the most exciting time to be working in neuroscience. At last it seems as though many of the secrets of the nervous system are yielding to research. The genes for the acetylcholine receptor, the sodium channel and the three opioid peptide precursors have all been cloned. The crucial role of molecular genetics within neuroscience is firmly established.

The new technology has demonstrated the ability of a handful of gene products to orchestrate a complex sequence of behaviour in the marine mollusc *Aplysia*. Rapid progress is also being made in understanding how specific gene products control development in the insect's nervous system, or regulate the switching of transmitter production in adult mammalian neurons. Undoubtably molecular genetics will have a major impact on clinical neuroscience during the 1980s.

A special subscription rate 30% below the personal subscription is available for all students (undergraduate, graduate, postgraduate) and neurology residents. The 1986 student subscription rate is UK £21.00; USA and Canada US$37.00; Europe 98.00 Dutch Guilders; Rest of World 107.00 Dutch Guilders. Student subscriptions must be accomplished by valid proof of student status.

Gene research in neuroscience is not the only area where activities are occuring at an explosive rate. PET studies of human cognitive function, computer monitoring of whole body and limb movement and psychophysical testing of perceptual activities are all contributing to our knowledge of higher brain functions in health and disease.

Trends in NeuroSciences is the only review journal which covers all aspects of neuroscience. Its unique style makes it accessible to researchers and students alike. Don't miss out on the excitement, subscribe to **Trends in NeuroSciences** today.

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The electroplax sodium channel revealed *William Catterall*

MPTP and Parkinson's disease *J. William Langston*

Are glial cells excitable after all? *Joan Abbott*

Homeotic gene expression in *Drosophila Michael, S. Levine and Cathy J. Wedeen*

How do growth cones grow? *Carol Mason*

Neural and molecular mechanisms underlying information processing in *Aplysia John H. Byrne*

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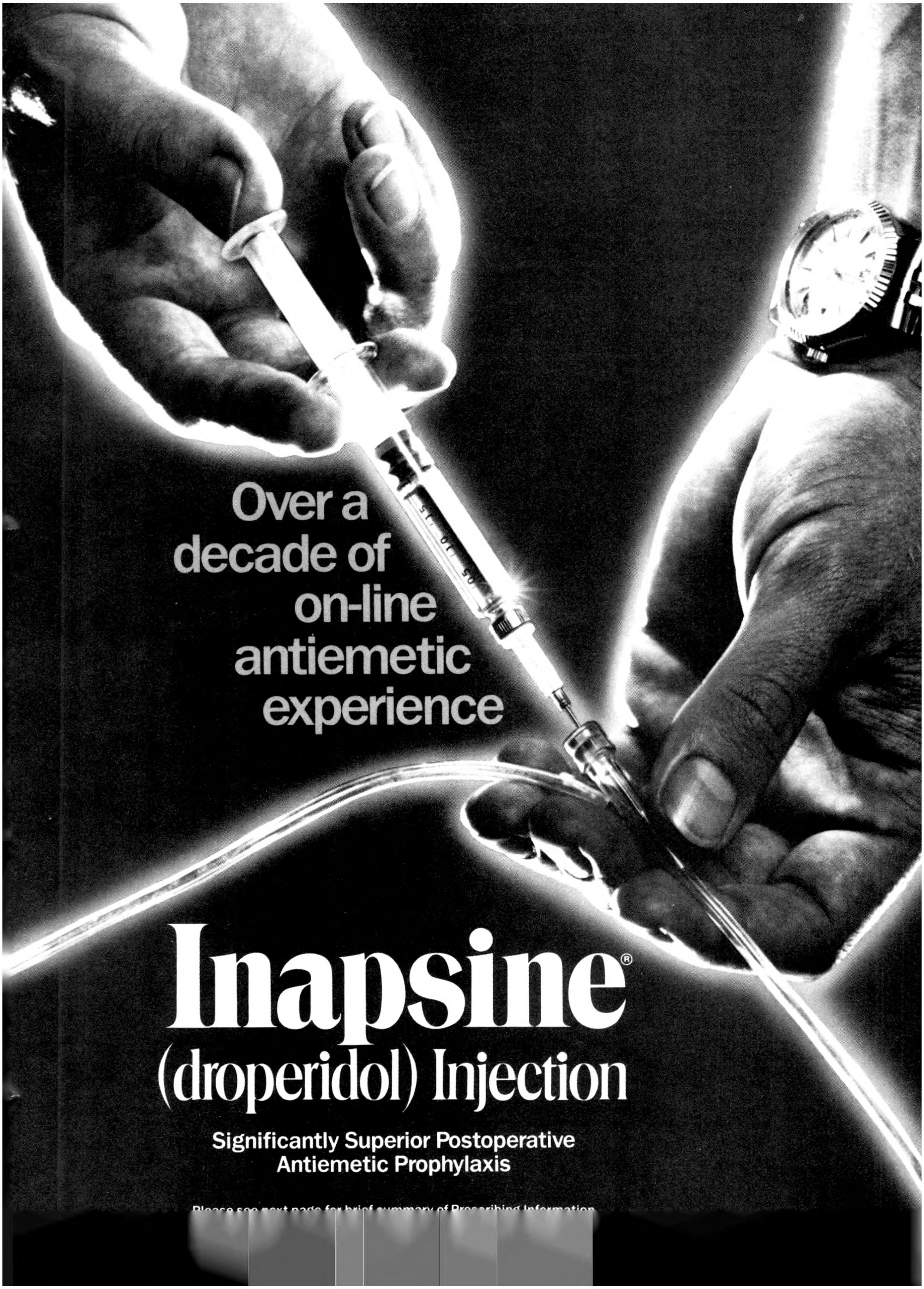

Over a decade of on-line antiemetic experience

Inapsine®

(droperidol) Injection

Significantly Superior Postoperative Antiemetic Prophylaxis

Please see next page for brief summary of Prescribing Information

Over a decade of on-line antiemetic experience

- ▶ Proven in double-blind studies to provide postoperative antiemetic effect (when given perioperatively) that is significantly superior to placebo,[1,2] diazepam[2] and hydroxyzine[2,3]
- ▶ Potent antiemetic activity extends through discharge from recovery room
- ▶ May be administered *intraoperatively* in long procedures as well as preoperatively in both long and short procedures
- ▶ Helps maintain cardiovascular stability by protecting against hypertensive episodes, heart rate changes and the pressor and arrhythmogenic effects of epinephrine
- ▶ Facilitates a comfortable, anxiety-free emergence, reducing the need for postoperative opioids

Inapsine®

(droperidol) Injection

Significantly Superior Postoperative Antiemetic Prophylaxis

Before prescribing please consult complete prescribing information, of which the following is a brief summary.
Protect from light. Store at room temperature.
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY.
Droperidol is a neuroleptic (tranquilizer) agent.

DESCRIPTION: *2 ml. and 5 ml. ampoules:* Each ml. contains Droperidol 2.5 mg. and lactic acid for pH adjustment to 3.4 ± 0.4
10 ml. vials: Each ml. contains Droperidol 2.5 mg. with 1.8 mg. methylparaben and 0.2 mg. propylparaben, and lactic acid for pH adjustment to 3.4 ± 0.4

INDICATIONS: INAPSINE (droperidol) is indicated: • to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures; • for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia; • in neuroleptanalgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE® (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE.
As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.

If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.

PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms, INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.

Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effect with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias. (See full prescribing information for complete description.)

ADVERSE REACTIONS: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).

When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur; if these remain untreated, respiratory arrest could occur.

Elevated blood pressure, with or without pre-existing hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

Usual Adult Dosage

I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.

II. Adjunct to General Anesthesia
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
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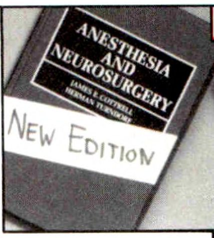

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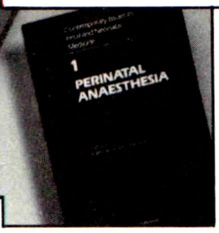

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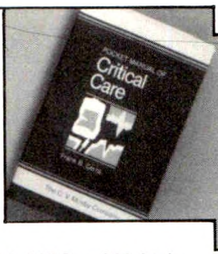

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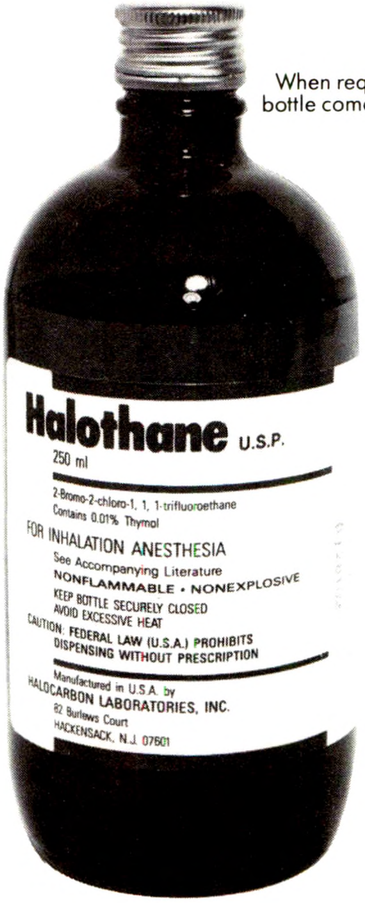
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Depression of Myocardial Contractility In Vitro by Bupivacaine, Etidocaine, and Lidocaine

Carl Lynch III, MD, PhD

LYNCH C III. Depression of myocardial contractility in vitro by bupivacaine, etidocaine, and lidocaine. Anesth Analg 1986;65:551–9.

The effects of local anesthetics in depressing myocardial contractility were studied in isolated guinea pig right ventricular papillary muscles. Bupivacaine and etidocaine, 4 and 10 μM, showed reverse frequency-dependent depression of contractility, that is, less significant depression of contractility at higher stimulation frequencies (2–3 Hz) than at lesser frequencies (<1 Hz). Lidocaine, 40 μM, demonstrated a similar trend. In contrast, the normal action potential maximum rate of depolarization ($\dot{V}_{max}$), a measure of sodium channel conductance, was significantly more depressed at 2–3 Hz by bupivacaine and etidocaine than by lidocaine. Consequently, contractile depression could be overcome only at higher stimulation frequencies, at which conduction was depressed. To explore the mechanism of the contractile depression, local anesthetic effects were studied on slow (calcium channel-mediated) action potentials in partially depolarized papillary muscles. Etidocaine and bupivacaine, 4 and 10 μM, and lidocaine, 40 and 100 μM, caused a marked depression of the late-peaking contractile responses, attributed to Ca^{2+} release from the sarcoplasmic reticulum. In contrast, only 10 μM bupivacaine caused any significant depression of the slow action potential rate of depolarization (to 89% of control), consistent with a possible small depression of Ca^{2+} entry.

Key Words: ANESTHETICS, LOCAL—bupivacaine, etidocaine, lidocaine. HEART—action potential, contractility.

In the clinical setting, cardiovascular collapse has been associated with intravenous bupivacaine and etidocaine (1–3). In vivo animal studies have suggested that the highly lipid-soluble local anesthetics, bupivacaine and etidocaine, cause more lethal myocardial dysfunction and dysrhythmias than lidocaine at equivalent local anesthetic doses (4–11). Recently, Clarkson and Hondeghem (12,13) have demonstrated that bupivacaine binds to and blocks inactivated sodium channels more tightly than lidocaine, leading to conduction blockade with higher frequencies of stimulation. Although the electrophysiologic basis of local anesthetic action is blockade of sodium channels, which results in conduction blockade, these compounds have cellular actions unrelated to sodium channel effects. Procaine and tetracaine directly inhibit Ca^{2+} release from the sarcoplasmic reticulum of skeletal muscle (14–16), and procaine and the local anesthetic SKF-525-A have been shown to inhibit Ca^{2+} release from isolated myocardial sarcoplasmic reticulum (17). The well-characterized effects of local anesthetics upon Ca^{2+} release by the sarcoplasmic reticulum or possible effects on Ca^{2+} entry into the cell could contribute to depression of myocardial contractile function. The present study was performed to examine how these actions, unrelated to the sodium channel, may contribute also to myocardial depression.

Methods

The heart was removed from guinea pigs (300–400 g) under diethyl ether anesthesia, and right ventricular papillary muscles were excised. Muscles were pinned by the cut end into the base of the chamber (25 × 5 × 3 mm), and the tendinous end was attached to a Series 400A Force Transducer System (Cambridge Technologies, Inc.). Muscle length was adjusted to the lowest rest tension at which maximum twitch tension was observed. Muscles were maintained at 37°C and superfused at a rate of 8 ml/min with standard Tyrode solution composed of Na, 143 mM; K, 4.7 mM; Cl, 128 mM; Ca, 2.5 mM; Mg, 2.0 mM; SO_4, 2.0 mM; HCO_3, 25 mM; glucose, 11 mM; EDTA, 0.1 mM. Solution circulated through the chamber from heated

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Supported in part by a grant from the American Society of Regional Anesthesia and from the National Institutes of Health, RO1GM331144-04.

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Address correspondence to Dr. Lynch, Department of Anesthesiology, University of Virginia Medical Center, Box 238, Charlottesville, VA 22908.

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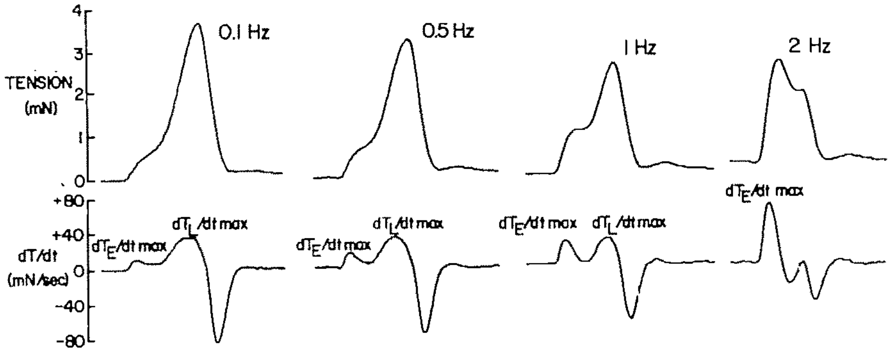

Figure 1. Contractions accompanying slow action potentials (upper panels), at various frequencies of stimulation, and the time differential of the tension trace (lower panels). The maximum rate of early tension development (dT_E/dt max) and the maximum rate of late tension development (dT_L/dt max) are the indicated peaks on the dT/dt tracing.

reservoir containers through which 95% O_2/5% CO_2 was bubbled, maintaining pH at 7.45 ± 0.5. The muscles were field-stimulated by stainless steel electrodes placed along the wall of the chamber. Stimuli were 0.5 msec in duration. In this present study, the muscle cross-sectional area was calculated from the muscle length, weight, and density, and ranged from 0.45 to 1.0 mm^2.

Muscles were impaled and intracellular potential monitored by conventional 3 M KCl-filled microelectrodes attached to a WPI VF-1 preamplifier. Bath potential, monitored through an agar bridge–Ag/AgCl electrode, was subtracted from the intracellular potential to give the membrane potential (V_m). Tension and its first derivative were continuously recorded on a Gould 440 recorder. Twitch tension, the action potential, and its first derivative ($\dot{V}$) were monitored on a Tektronix D11 storage oscilloscope. The resting membrane potential, action potential amplitude, action potential duration to 90% repolarization, and the maximum rate of depolarization ($\dot{V}_{max}$) were recorded directly or from photographic records. The normal action potential $\dot{V}_{max}$ was employed as a quantitative estimate of inward current through the sodium channel (I_{Na}). Tension response and action potentials were also recorded on a Tektronix 5D10 wave-form digitizer and subsequently plotted on an X-Y recorder for analysis.

A protocol of stimulation was employed in which, after 15 min rest, a rested state contraction was elicited, followed by stimulation rates of 0.1, 0.25, 0.5, 1.0, 2.0, and 3 Hz applied sequentially. Each stimulation rate was maintained until a steady state and unchanging contraction was achieved before proceeding to the next higher frequency. All muscles showed a typical positive treppe or staircase, in which the steady-state contractile response was larger at each higher stimulation frequency. Maximum peak tensions were observed at 3 Hz and ranged from 1 to 7 mN (milliNewton, equivalent to the force exerted by gravity on a mass of 102 mg). After control studies, muscles were exposed to anesthetics for at least 15 min prior to the recording of responses, which was found to be sufficient time for a stable constant drug effect. Recovery responses were recorded at least 30 min after washout of anesthetic from the chamber. Intracellular recording was attempted in all experiments, but the vigorous contractions observed at higher stimulation frequencies often caused dislodgement of the microelectrode. Changes in action potential characteristics were analyzed in those settings in which intracellular impalements were maintained throughout the control, drug exposure, and recovery periods. Because action potential $\dot{V}_{max}$ may vary slightly with the action potential latency, stimulation intensity occasionally required adjustment to maintain the same latency between the stimulus and the action potential depolarization for each stimulation frequency. This latency was then maintained throughout the drug exposure and recovery periods. Each drug concentration was studied in four to seven individual muscles. Four and ten micromolar concentrations of bupivacaine and etidocaine were used, corresponding respectively to 1.15 and 2.88 μg/ml for bupivacaine and 1.11 and 2.76 μg/ml for etidocaine. A 40-μm concentration of lidocaine was used, corresponding to 9.37 μg/ml.

Membrane action potentials and muscle contractions were also studied in muscles that were partially depolarized to −40 to −45 mV in 26 mM potassium Tyrode (potassium substitution for an equivalent concentration of sodium to maintain the calculated osmolality). Isoproterenol (0.1 μM) was added to elicit slow action potentials, mediated by current through the slow (calcium) channel, with typical maximum rates of rise ($\dot{V}_{max}$) of 15–25 V/sec. Slow action potential $\dot{V}_{max}$ was employed as an estimate of slow inward (calcium) current (18). Furthermore, with stimulation after rest and up to frequencies of 0.5 Hz, these partially depolarized muscles show a late-peaking tension response similar to the adrenergically-stimulated rested state contraction in normal Tyrode. This late-peaking contraction is attributed to Ca^{2+} flux into the cell that is taken into the sarcoplasmic reticulum and

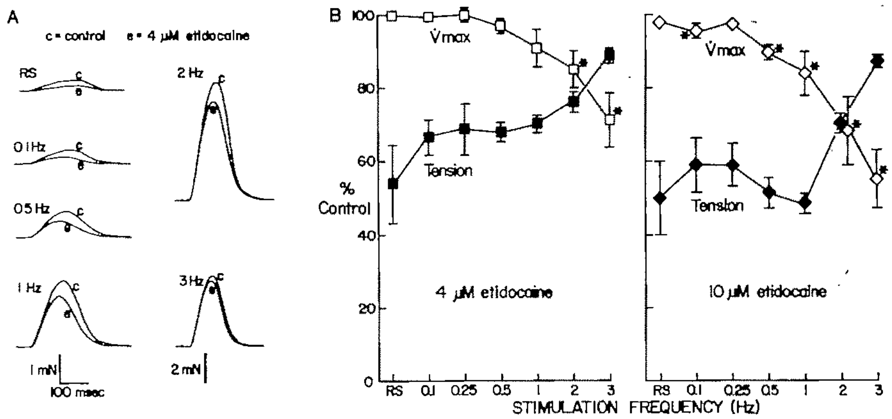

Figure 2. Effects of etidocaine on myocardial performance. (**A**) Steady state contractile responses at the indicated frequency under control conditions (c) and in the presence of 4 μM (1.11 μg/ml) etidocaine (e). Calibration bar at right applies only to 3-Hz responses. Washout of drug resulted in incomplete recovery (not shown). RS, rested state. (**B**) Effects of 4 and 10 μM (2.76 μg/ml) etidocaine on peak tension (filled symbols) and normal action potential rate of depolarization ($\dot{V}_{max}$, open symbols) at various frequencies of stimulation. Steady-state responses with etidocaine were expressed as the percent of the steady-state control response observed at the same frequency. Results plotted are mean ± SEM percent of control peak tension from five different muscles, and mean ± SEM percent of control $\dot{V}_{max}$ in four muscles in which impalements were maintained (average control $\dot{V}_{max}$: 188 ± 6 V/sec). All values of tension were significantly reduced from control. Contractions at RS, 0.1 Hz, and 0.5 Hz were depressed more than those at 2–3 Hz with 4 μM etidocaine; contractions at RS up to 2 Hz were depressed more than at 3 Hz with 10 μM etidocaine. *Indicates significant change in $\dot{V}_{max}$ from control.

then subsequently released near the end of the action potential depolarization (19). Figure 1 shows the typical contractions accompanying slow action potentials in 26 mM K^+ Tyrode with 0.1 μM isoproterenol. Tension responses at 0.1 (identical to rested state), 0.5, 1, and 2 Hz are in the upper panels, with the time differential (dT/dt) of the tension response shown below. From the rate of tension development, the maximum rate of early tension development (dT_E/dt max) and the maximum rate of late tension development (dT_L/dt max) were measured as indicated by the peak on the dT/dt tracing. No late-peaking tension development consistently occurred at 2–3 Hz, and no value of dT_L/dt max was noted. The magnitude of this late-peaking tension is comparable to the peak tension observed in normal Tyrode at 3 Hz stimulation (1–6 mN).

These preparations show stable, reproducible performance for 2–8 hr, with changes because of aging being less than 10% during the period from control to drug application through washout and recovery. In previous studies, recovery to control levels was observed following exposure to volatile anesthetics, and results were expressed as the percent of the average control and recovery value (20,21). Measurements during local anesthetic exposure are expressed only as a percent of the control observation because complete recovery of control tension was not consistently observed after washout of the local anesthetics. Such incomplete recovery, seen particularly with etidocaine and bupivacaine, was attributed to incomplete washout of drug.

Testing for significant differences ($P < 0.05$) in tension and normal action potential characteristics among the stimulation frequencies or among the anesthetic concentrations for each variable was carried out by one-way analysis of variance, as was significance of drug effect versus control. Change from the control slow action potential $\dot{V}_{max}$ by local anesthetics was tested by paired *t*-test.

Results

Normal Action Potential Experiments

Figure 2*A* shows the control steady-state tension responses after rest (RS) and from 0.1 up to 3 Hz; the steady-state responses observed in the presence of 4 μM (1.11 μg/ml) etidocaine at each frequency are superimposed. A late component of tension development, prominent after rest and up to 0.5 Hz, was depressed by etidocaine, but the early-peaking tension at 2–3 Hz was well-preserved. The peak rate of tension development (dT/dt max) which occurred initially was only modestly depressed, and thus the depression of peak tension was due primarily to reduction of the later rate of tension development. The average percent depression of peak tension by 4 and 10 μM etidocaine as a function of frequency is shown in Figure 2*B* (filled symbols). Contractility as measured by peak tension was significantly less depressed at 3 Hz than at rest (RS), 0.5 Hz, and 1.0 Hz. Depression of dT/dt max (not plotted) did not vary significantly with frequency. Although increasing frequency of stimulation counteracted the depressant contractile effects of etidocaine, the rate of depolari-

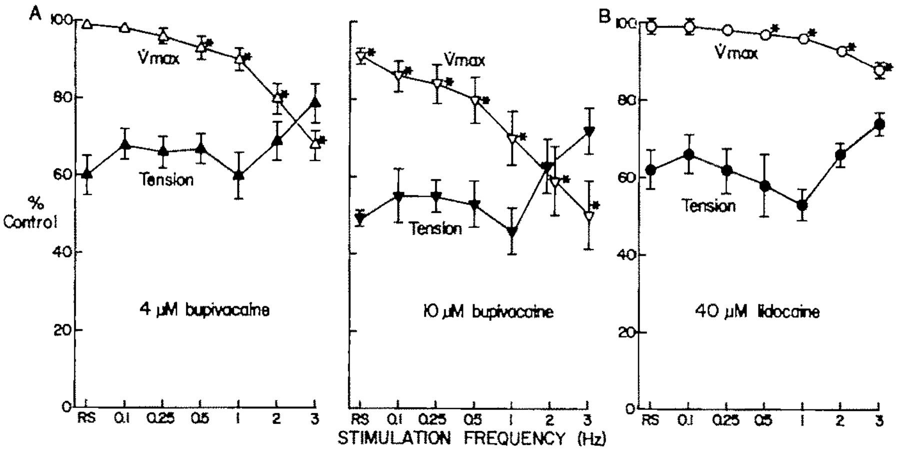

Figure 3. Effects of bupivacaine and lidocaine on myocardial performance. Steady-state responses in the local anesthetic were expressed as the percent of the control response observed at the same frequency. Values plotted are mean ± SEM percent of control peak tension (filled symbols), and mean ± SEM percent of control $\dot{V}_{max}$ (open symbols). Tension was significantly depressed by both bupivacaine and lidocaine at all frequencies. *indicates significant change in $\dot{V}_{max}$ from control. (A) Four micromolar (1.15 µg/ml) caused significantly greater peak tension depression at rested state and 1 Hz than at 3 Hz (n = 6). Ten micromolar (2.88 µg/ml) bupivacaine depressed peak tension significantly more at rested state, and at 0.25 Hz up to 1 Hz, than at 3 Hz (n = 5). Control $\dot{V}_{max}$ in muscles in which impalements were maintained was 215 ± 31 V/sec (±SEM, n = 5). (B) Forty micromolar (9.37 µg/ml) lidocaine significantly depressed peak tension more at rested state, and at 0.25 up to 2 Hz, than at 3 Hz (n = 4). Control $\dot{V}_{max}$ in muscles in which impalements were maintained was 202 ± 27 V/sec (± SEM, n = 5). Lidocaine caused significantly less depression of $\dot{V}_{max}$ at 2 and 3 Hz than did bupivacaine or etidocaine (see Figure 2B).

Table 1. Local Anesthetic Effects on Slow Action Potential $\dot{V}_{max}$

Condition	n	Stimulation frequency (Hz) 0.25	1.0	2.0
Control	6	24.5 ± 4.9	21.6 ± 4.2	15.5 ± 3.5
4 µM bupivacaine		22.8 ± 4.3	21.9 ± 4.7	15.1 ± 3.5
Control	6	21.5 ± 4.3	18.3 ± 2.5	12.3 ± 1.0
10 µM bupivacaine		18.7 ± 4.6[a]	16.3 ± 2.3[a]	11.0 ± 1.3
Control	5	18.9 ± 4.5	15.5 ± 4.1	13.8 ± 4.7
10 µM etidocaine		16.1 ± 3.3	13.4 ± 3.0	10.9 ± 2.6
Control	4	19.8 ± 6.1	23.6 ± 6.0	22.8 ± 6.4
40 µM lidocaine		22.2 ± 7.0	25.5 ± 6.9	24.1 ± 7.5

Results are expressed in V/sec.

[a] $P > 0.05$ difference from control by paired t-test.

zation of the normal action potential ($\dot{V}_{max}$) was depressed increasingly as frequency increased from 1 to 3 Hz (Fig. 2B, open symbols). This effect is consistent with a frequency-dependent blockade of sodium channels by etidocaine as previously described (22).

The effects of 4 and 10 µM bupivacaine (Fig. 3A) are very similar to the equivalent concentrations of etidocaine. With increasing frequency of stimulation, the depressant effects of the drug on contractility were reduced. However, a dose- and frequency-dependent depression of $\dot{V}_{max}$ by bupivacaine was observed as previously described by Courtney (22) and by Clarkson and Hondeghem (12,13).

Lidocaine also caused contractile depression, which was more profound at low frequency (Fig. 3B). Across the frequency range studied, 40 µM lidocaine caused a pattern of depression that was similar to that of the tenfold lower concentration of the more lipid-soluble drugs. However, the frequency-dependent depression of $\dot{V}_{max}$ caused by 40 µM lidocaine was less profound than that observed with bupivacaine and etidocaine. Although $\dot{V}_{max}$ was significantly reduced by lidocaine at 0.5–3 Hz, the magnitude of this frequency-dependent depression was significantly less than that observed with 4 µM bupivacaine (at 2 and 3 Hz), 10 µM bupivacaine (at 0.5 to 3 Hz), or with 10 µM etidocaine (at 2 and 3 Hz).

With regard to action potential duration, lidocaine caused a significant decrease (93 ± 1% to 96 ± 1% of control) at all frequencies up to 2 Hz. Bupivacaine and etidocaine caused a similar effect, but the reduction was not uniformly significant at all frequencies.

Slow Action Potential Experiments

In order to better define the mechanism of action of these local anesthetics, the depressant effects on the slow action potential characteristics and the accompanying contractions were measured after rest and up to 3 Hz stimulation. Table 1 summarizes the effects of etidocaine, bupivacaine and lidocaine on slow action potential $\dot{V}_{max}$ at 0.25, 1, and 2 Hz. The values are expressed as percent of control. As apparent from the average control values, the slow action potential

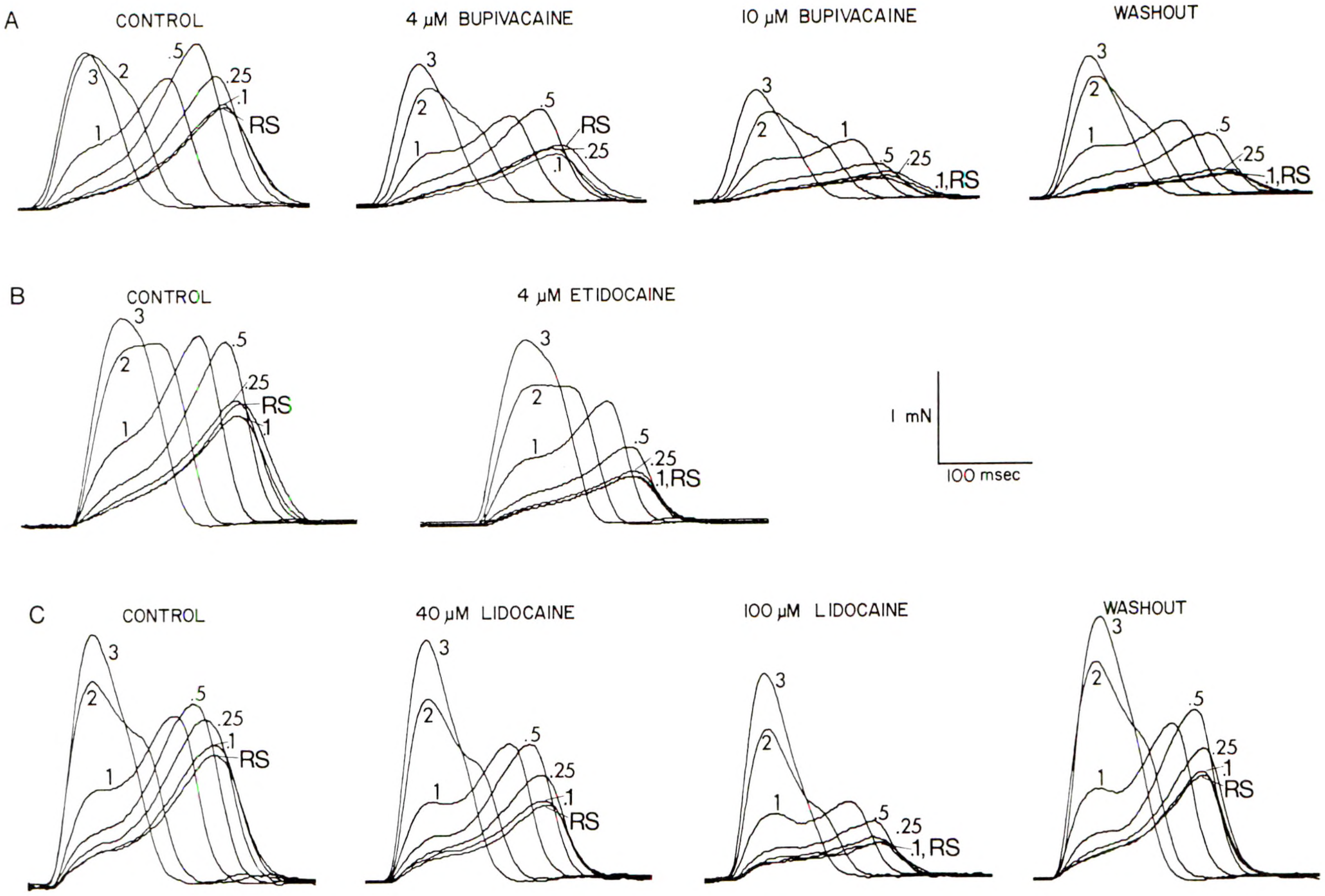

Figure 4. Local anesthetic depression of papillary muscle contractions associated with isoproterenol-induced slow action potentials. Contractile responses at the various frequencies under each indicated condition are superimposed. The number beside each trace indicates the frequency of stimulation (in Hz) at which that steady state response was recorded. RS, rested state contraction. (**A**) Effects of 4 and 10 μM bupivacaine on contractile responses, and subsequent recovery after 40 min washout. (**B**) Effects of 4 μM etidocaine. Incomplete recovery to control responses accompanied washout (not shown). (**C**) Effects of 40 and 100 μM lidocaine, with complete recovery to control accompanying washout.

$\dot{V}_{max}$ frequently showed a characteristic frequency-dependent decline in the absence of drug application. Ten micromolar bupivacaine significantly depressed slow action potential $\dot{V}_{max}$ at 0.25 and 1 Hz in six muscles by 13 and 11%, respectively. Lidocaine, 40 μM, 10 μM etidocaine, and 4 μM bupivacaine caused no significant depression. At 3 Hz, action potential latency was difficult to maintain with accuracy, so $\dot{V}_{max}$ values are not tabulated. However, there did not appear to be any prominent depression of slow action potential $\dot{V}_{max}$ by these drugs at 3 Hz. During washout of drug, partial or complete recovery of $\dot{V}_{max}$ was observed. Slow action potential amplitude and duration were not significantly altered by these anesthetics.

In contrast to the small effects of these local anesthetics on slow action potential characteristics, effects on the contractile behavior were far more profound and frequency-dependent. Figure 4 shows superimposed steady state contractile responses for each frequency as indicated. Bupivacaine (Fig. 4*A*) caused marked dose-dependent depression of the late peak tension after rest and at stimulation frequencies from 0.1 to 1 Hz. Whereas the rapidly peaking tension at 2–3 Hz was mildly depressed, the effect on the late peak tension was far more dramatic. With washout of the 10-μM concentration of drug, partial recovery was observed. Figure 4*B* demonstrates the frequency-dependent depression of the late-peaking tension by 4 μM etidocaine, from which recovery with washout was incomplete (not shown). Figure 4C demonstrates the effects of 40 and 100 μM lidocaine upon slow action potential contractions. The late-peaking tension is preferentially depressed by lidocaine in a fashion similar to bupivacaine and etidocaine. In contrast to bupivacaine and etidocaine, depressant effects of lidocaine were more readily reversed by washing out the drug, as shown here.

Figure 5*A* plots the effects of bupivacaine upon

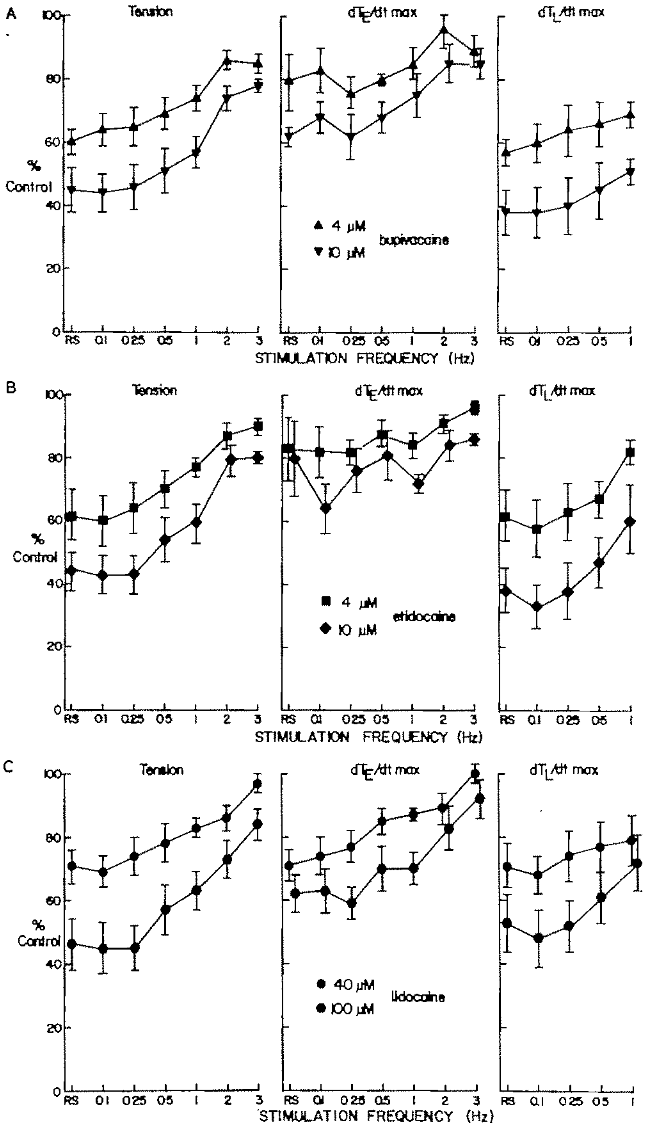

Figure 5. Effects of local anesthetics on peak tension, dT_E/dt max, and dT_L/dt max at various stimulation frequencies. Mean values ± SEM, expressed as percent of control, are plotted versus frequency. (A) Effects of bupivacaine ($n = 7$). (B) Effects of etidocaine ($n = 5$). (C) Effects of lidocaine ($n = 5$).

peak tension, the maximum rate of early tension development (dT_E/dt max), and the maximum rate of development of late-peaking tension (dT_L/dt max). Results, expressed as percent of the control response, represent the mean of seven muscles studied. The average effect of etidocaine observed in five muscles is plotted in Figure 5*B*. Each concentration of both drugs caused significantly greater depression of late-peaking tension in the rested state up to 1 Hz than of the early-peaking tension at 2–3 Hz stimulation. As shown in Figure 5C, lidocaine had effects similar to the more lipid-soluble compounds, causing significantly greater depression from rested state to 0.5 Hz than at 3 Hz stimulation frequency. These local anesthetics significantly depressed the maximum rate of late tension development (dT_L/dt max) at all frequencies (not measured beyond 1 Hz). At each frequency up to 1 Hz, etidocaine (4 and 10 μM) and bupivacaine (10 μM) caused significantly greater depression of dT_L/dt max than of dT_E/dt max. While etidocaine and bupivacaine show equivalent effects at equal concentrations, approximately ten times greater concentrations of lidocaine were required to effect an equivalent degree of depression.

The effects of the amide local anesthetics were also compared to those of procaine, an ester local anesthetic known to inhibit release of Ca^{2+} by myocardial sarcoplasmic reticulum (17). Figure 6 shows the effects of 400 μM procaine upon slow action potential contractions. As with the amide local anesthetics, this ester local anesthetic causes selective depression of the late-peaking tension, with less depression of the early-peaking tension at 2–3 Hz. A late component of tension present at 2–3 Hz is also greatly reduced.

Discussion

The local anesthetics in this study caused a reverse frequency-dependent depression of myocardial contractility, depressing tension development more at low frequencies of stimulation. These effects on myocardial contractility contrast sharply with local anesthetic effects on the rate of depolarization of the fast action potential, which is a measure of sodium ion influx through sodium channels. The normal action potential $\dot{V}_{max}$ is increasingly depressed by lidocaine and bupivacaine as stimulation frequency is increased, demonstrating the frequency- or use-dependent blockade of sodium channels (12,13,22). However, bupivacaine causes prominent blockade at far lower stimulation frequencies than lidocaine, which is attributed to tighter binding of bupivacaine to inactivated sodium channels (12,13). Similar effects upon the fast action potential $\dot{V}_{max}$ were observed in this study with bupivacaine and etidocaine, although the degree of depression by 4 and 10 μM bupivacaine at 1–3 Hz appears to be somewhat less than that observed by Clarkson and Hondeghem (12,13). The more profound effect seen by these workers may be due to the use of HEPES buffer, which enhances local anesthetic blockade of sodium channels by causing partial depolarization (23). The very similar effects observed for etidocaine would be expected based on earlier experiments by Courtney (22), who found that recovery from use-dependent sodium channel blockade by bupivacaine and etidocaine required a longer interval than required by lidocaine.

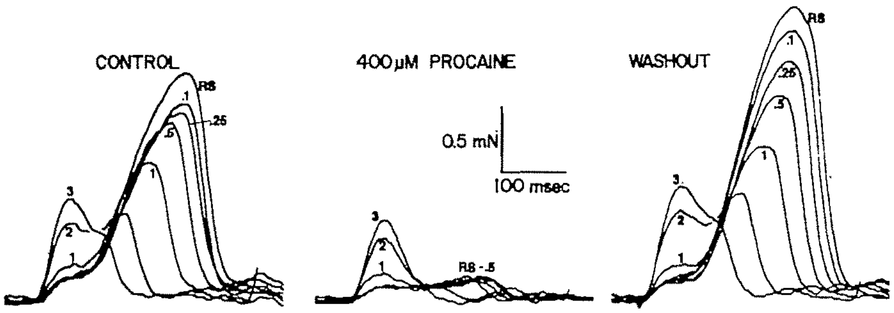

Figure 6. Procaine depression of papillary muscle contractions associated with isoproterenol-induced slow action potentials. Contractile responses at various frequencies of stimulation (in Hz) are superimposed.

The prolonged sodium channel binding of bupivacaine can cause slowed intramyocardial conduction, which may lead to reentrant conduction circuits (16) and account for the ventricular dysrhythmias, tachycardia, and fibrillation observed clinically (1,3) and experimentally in vivo (4,6,10,11). Slowing of atrioventricular conduction in isolated heart preparations with eventual conduction block is described with increasing concentrations of bupivacaine and etidocaine, and also by tenfold greater concentrations of lidocaine (24,25). Recently Hotvedt et al. (26), while examining the effects of bupivacaine on cardiac electrophysiologic behavior of the dog in vivo, found that the atrial–His bundle (AH) interval was increased even more than the His bundle–ventricular (HV) interval at concentrations of 2000–2500 ng/ml plasma concentration. The use-dependent blockade of sodium channels by bupivacaine probably mediates the AH, His bundle–ventricular and intraventricular conduction defects observed with this drug. However, because AH conduction is mediated in part by Ca^{2+}-dependent slow action potentials in the AV node, it is possible that the modest slow channel blocking properties of bupivacaine might contribute also to disruption of AV conduction at toxic concentrations.

Although ventricular dysrhythmias and fibrillation have been frequently observed in patients (1,3) and in animal studies (4,6,10,11) in which toxic doses of bupivacaine have been administered, electromechanical dissociation has also frequently been observed, particularly accompanying bradycardia (5,27). The in vitro experiments in this study provide evidence for myocardial contractile dysfunction with low heart rates. As higher stimulation frequencies are employed, the contractile depression is far less profound. Field stimulation of papillary muscles in an experimental chamber, as in this study, permits uniform contractions to be maintained at higher stimulation frequencies. The amount of tissue is small, and all of it is subjected to the electrical field and is depolarized to initiate an action potential. Action potential conduction over long distances within the tissue is not required. In intact animals, however, decreases in sinus rate, AV conduction disturbances, and intraventricular conduction disturbances may prevent maintenance of high heart rates, thus allowing the depressant effects of etidocaine and bupivacaine observed at lower heart rates to become apparent. In this study, lidocaine at concentrations of 40 and 100 μM (9.37 and 23.4 μg/ml) had contractile depressant properties equivalent to 4 and 10 μM bupivacaine (1.15 and 2.88 μg/ml), respectively. However, in vivo lidocaine permits AV and myocardial conduction at higher frequencies or heart rates at which myocardial contractility is less depressed.

The results of this study agree with previous work (24,28), in which a ten times greater concentration of lidocaine was necessary to cause depression of cardiac contractions comparable to bupivacaine. Tanz et al. (28) demonstrated in isolated guinea pig heart that 9.2 μM (3 μg/ml) bupivacaine depressed contractility more than 111 μM lidocaine (30 μg/ml). In that study, in which heart rate was not controlled, bupivacaine caused a significantly greater reduction in heart rate than lidocaine, which further emphasizes the depressant effects of bupivacaine. The tenfold difference in contractile depressant properties between lidocaine and bupivacaine contrasts with only two to fourfold greater potency of bupivacaine over lidocaine in depressing axonal conduction (29). The results described in this present study are different from those of Clarkson and Hondeghem (13), who found that the depression by bupivacaine of the peak tension developed by guinea pig papillary muscle did not vary significantly with frequency. In that study, contractions accompanying normal action potentials were studied in a solution buffered with 1 mM HEPES, which may alter mechanical performance (30).

Reiter et al. (19) have concluded that the late-peaking tension observed with isoproterenol stimulation in myocardium is due to uptake and subsequent release of Ca^{2+} by myocardial sarcoplasmic reticulum (SR). Stimulation by β-adrenergic compounds enhances uptake into myocardial SR of calcium by a cAMP stimulated Ca^{2+}-dependent ATPase ("Ca^{2+} pump") (31). If this late tension peak is due to SR release, compounds such as local anesthetics, which depress SR Ca^{2+} release might be expected also to depress the late peak. The local anesthetics procaine and SKF 525-A have been found to inhibit Ca^{2+}-induced Ca^{2+} release from purified cardiac SR vesicles (17), and procaine is now shown to depress this late tension peak attributed to SR Ca^{2+} release. This late-peaking tension response can also be depressed by Ca^{2+} entry blocking agents such as nifedipine. Bupivacaine demonstrated only modest depression of the rate of depolarization of slow action potentials, presumably dependent upon Ca^{2+} entry through the slow channel. The profound depression of late-peaking tension was observed with concentrations of bupivacaine and etidocaine in the absence of significant depression of slow action potential $\dot{V}_{max}$, and suggests an effect upon a mechanism distinct from Ca^{2+} entry. Because these depressant effects occur in partially depolarized muscles in which sodium channels are inactivated, these effects are unlikely to be related to the local anesthetic sodium channel effects. The depression by etidocaine, bupivacaine, and lidocaine of the procaine-sensitive late peak tension suggests that these local anesthetics directly depress myocardial contractility by alteration of Ca^{2+} release from the SR.

In summary, the local anesthetics appear to possess intrinsic abilities to depress myocardial contraction at low frequencies, possibly by interfering with Ca^{2+} release from the sarcoplasmic reticulum. Because of their potent use-dependent blockade of sodium channels, the highly lipid-soluble local anesthetics, bupivacaine and etidocaine, also block intraventricular conduction at high stimulation frequencies or heart rates. These combined actions probably explain the more profound myocardial depressant effects observed with these drugs as compared with lidocaine.

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Increased Norepinephrine Release from Dog Pulmonary Artery Caused by Nitrous Oxide

Duane K. Rorie, MD, PhD, Gertrude M. Tyce, PhD, and John C. Sill, MBBS

RORIE DK, TYCE GM, SILL JC. Increased norepinephrine release from dog pulmonary artery caused by nitrous oxide. Anesth Analg 1986;65:560–4.

The effects of nitrous oxide on the release and metabolism of norepinephrine (NE) at neuroeffector junctions in dog pulmonary artery were examined. Helical strips of artery were incubated in Krebs–Ringer solution containing L-(^{3}H)NE and mounted for superfusion. The arterial strips were studied in the presence of 1) 95% oxygen–5% carbon dioxide, 2) 70% nitrogen–30% oxygen, or 3) 70% nitrous oxide–30% oxygen. During the 60 min of each experiment, five samples of superfusion fluid were collected for analysis and the effluxes of (^{3}H)NE and its radiolabeled metabolities were measured before and during electrical stimulation and during recovery from stimulation. (^{3}H)Norepinephrine was separated from its metabolites in the superfusate and in extracts of artery by column chromatography and quantitated by liquid scintillation spectrometry. Nitrous oxide significantly increased the fractional loss of total radioactivity and the amount of NE in the superfusate both during resting conditions and during stimulation. Nitrous oxide had no effect on the proportions of radioactivity among metabolites of NE in the superfusate or on the profile of NE metabolites remaining in the tissue after experimentation. These findings are consistent with increased NE release as a direct effect of nitrous oxide on nerve endings.

Key Words: ANESTHETICS, GASES—nitrous oxide. SYMPATHETIC NERVOUS SYSTEM—nitrous oxide.

Several studies have shown increased pulmonary vascular resistance concurrent with the administration of nitrous oxide (1–4), although other studies do not support this finding (5–7). The variability in findings may be attributed to differing conditions at the time nitrous oxide was administered, to different anesthetic backgrounds, or in some instances, to preexisting impairment of the circulatory system, including the presence of valvular heart disease (2,3) or elevated pulmonary vascular resistance (2,4). The pulmonary vasoconstrictive action of nitrous oxide seems more likely to be encountered when there are pathologic changes in the circulatory system (2,4,8). Reversal of the vasoconstrictive effect of nitrous oxide by the administration of the α-blocker phentolamine suggests that the sympathetic nervous system may be involved in this action by nitrous oxide (8). How nitrous oxide activates the sympathetic nervous system is unknown, although signs of sympathetic nervous system activation have been reported in human beings, dogs, and cats when nitrous oxide has been given (9–12). The present studies were designed to determine whether nitrous oxide might be causing pulmonary vasoconstriction by increasing release of norepinephrine (NE) or by increasing synaptic concentrations of NE by an effect on metabolism of NE after its release.

Methods

Collection and Superfusion of Pulmonary Arteries

Mongrel dogs (15–25 kg) of both sexes were anesthetized with intravenous pentobarbital (30 mg/kg). The thorax was opened, and the trachea, lungs, and heart removed en bloc. Lung parenchyma was removed from small tertiary arteries (2–4 mm diameter) selected randomly throughout the lung. Each artery was cut into a helical strip. The helical strips were incubated for 1 hr in Krebs–Ringer solution containing (^{3}H)NE (2×10^{-7} M). The preparations were then suspended and superfused with Krebs–Ringer solution (13) at 2 ml/min in a constant-temperature, en-

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Address correspondence to Dr. Rorie, Department of Anesthesiology, Mayo Clinic, Rochester, MN 55905.

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closed superfusion chamber. Contractile tensions were measured by attaching the upper end of the vessel strip to a force-displacement transducer. The composition of the Krebs–Ringer solution was: NaCl, 118.3 mM; KCl, 4.7 mM; $MgSO_4$, 1.2 mM; $CaCl_2$, 2.5 mM; $NaHCO_3$, 25.0 mM; glucose, 11.1 mM; and calcium disodium EDTA 0.026 mM. Krebs–Ringer solution made with this formula is normally aerated with premixed 95% oxygen–5% carbon dioxide and has a pH of 7.40–7.45. When a high concentration of nitrous oxide or nitrogen is added to the premixed 95% oxygen–5% carbon dioxide aerating gas, alteration in carbon dioxide tension occurs and the pH increases to >8.0. To prevent the upward shift in pH, the formula for preparing the Krebs–Ringer solution was modified as described by Naito and Gillis (14). The ionic concentration and osmotic pressure of the modified Krebs–Ringer solution are very close to those of regular Krebs–Ringer solution and, when aerated with 70% nitrogen–30% oxygen or 70% nitrous oxide-30% oxygen, the pH was 7.40–7.42.

In the studies described here, the superfusion fluid was pre-aerated with one of three gases: 1) 70% nitrous oxide–30% oxygen, 2) 70% nitrogen–30% oxygen or 3) 95% oxygen–5% carbon dioxide. The gas used to aerate the superfusion fluid also filled the superfusion chamber. At the beginning of each study, a 90–min washout and equilibration period was allowed for each artery before samples of superfusate were collected for analysis.

For electrical stimulation of adrenergic nerve endings, two platinum wires (0.5 mm diameter) were placed parallel to and in contact with the tissues; both strips and electrodes were superfused continuously. Electrical stimulation consisted of rectangular impulses (10 V, 2-msec duration, 2 Hz) provided by a direct current power supply and a switching transistor triggered by a Grass stimulator. Preliminary studies showed that this stimulation was supramaximal.

In each experiment the superfusate was collected continuously over 60 min. Sample 1 was collected in the 6 min before electrical stimulation, sample 2 was collected during the 18 min of continuous electrical stimulation, sample 3 was collected during the 18-min interval immediately after electrical stimulation, sample 4 was collected in the ensuing 12 min, and sample 5 was collected in the last 6 min of the experiment. Changes in the efflux of (^{3}H)NE and its metabolites with time were studied in the samples of superfusate.

At the end of the experiments, arteries were blotted dry, weighed, and immersed immediately for two 30-min periods in separate 5 ml aliquots of 1N acetic acid containing 0.03 mM disodium EDTA and 0.2 mg/ml ascorbic acid for extraction of total radioactivity.

Column Chromatography

(^{3}H)Norepinephrine was separated from its metabolites in the superfusate by the method of Graefe et al. (15). Carrier substances, 0.1 mg each of NE, normetanephrine (NMN), 3,4-dihydroxymandelic acid (DOMA), 3,4-dihydroxyphenylglycol (DOPEG), 3-methoxy-4-hydroxymandelic acid (VMA), and 3-methoxy-4-hydroxyphenylglycol (MHPG), 0.02 mg of disodium metabisulfite, and 0.4 ml of 2N hydrochloric acid were added for each 12-ml sample of superfusate and to each extract of artery. The average recovery of 10 ng of (^{3}H)NE added to extracts of superfusate was 86.23 ± 1.41% (mean ± SE; $n = 10$). The precision of the method was tested by performing ten determinations of the amount of (^{3}H)NE and the metabolites of (^{3}H)NE present in the same sample of superfusate collected during and immediately after electrical stimulation. The coefficients of variation for measurements of (^{3}H)NE and the metabolities of (^{3}H)NE were: NE, 6.20%; DOPEG, 1.02%; NMN, 6.70%; OMDA, 2.02%; and DOMA, 8.78% (16).

Radioactive Measurements

Aliquots (1 ml) of superfusate and of the effluents and eluates were added to 10 ml of Safety Solve (Research Products International), and the radioactivity was measured in a liquid scintillation counter. Corrections for quenching were made with an external standard. The average counting efficiency was 35%. Samples were counted for 10 min or long enough to reach 10,000 counts.

Fractional Release Calculation

The fractional rate of loss of radioactivity from the artery per time period was calculated by dividing the radioactivity in each superfusate by that present in the tissue. The amount of tritium in the tissue at any given time was calculated by adding to the amount of radioactivity remaining in the artery at the end of the study all the tritium collected in samples of superfusate from that time to the end of the sample collection.

Analysis of Data

All data are expressed on the basis of an artery weight of 100 mg to correct for variations in tissue weight. The mean weight of the tissues was 98.2 ± 1.4 mg (±SE; $n = 15$).

The data are expressed as means ± SE. Statistical analyses of the data were performed with a two-way analysis of variance and a Student's *t*-test; *P* values less than 0.05 were considered significant.

Materials

L-[Ring-2,5,6-^{3}H] norepinephrine with a specific activity of 45 Ci/mmol obtained from New England Nuclear (NET 678) was used in the experiments.

Results

Fractional Release of Total Radioactivity from Arteries During Superfusion

The fractional release of radioactivity from arteries into superfusate of tissues studied in oxygen–carbon dioxide was not different from that of tissues studied in nitrogen and oxygen during the resting conditions preceding electrical stimulation, during electrical stimulation, or during the reestablishment of resting conditions following electrical stimulation (Fig. 1). In the group of tissues studied in nitrous oxide and oxygen, the fractional release of radioactivity was significantly greater during electrical stimulation and immediately afterwards than during the corresponding time periods in either of the other two groups of arteries.

The Efflux of (^{3}H)NE and Radiolabeled Metabolites of NE from Pulmonary Artery during Resting Conditions in the Presence of Oxygen–Carbon Dioxide, Nitrogen–Oxygen, or Nitrous Oxide–Oxygen

To determine whether nitrous oxide might also affect other NE dynamics at the neuroeffector junction (e.g., neuronal uptake of NE, extraneuronal uptake of NE, or the metabolism of NE), all of the superfusate collected throughout each experiment was subjected to column chromatography; unmetabolized NE was separated from the metabolites of NE, and each was quantitated. In addition, the radioactivity remaining in the tissues at the end of the experiments was extracted and fractionated by column chromatography into NE and the metabolites of NE.

In the presence of oxygen and carbon dioxide (^{3}H)NE contributed only a small amount to the total tritium content of the superfusate collected from arteries during resting conditions preceding stimulation; the majority of the tritium was present as the metabolites of (^{3}H)NE (Fig. 2). The most prevalent metabolite during resting conditions was (^{3}H)DOPEG, followed by (^{3}H)OMDA (*O*-methylated-deaminated compounds, a mixture of (^{3}H)VMA and (^{3}H)MHPG); similar amounts of (^{3}H)NMN and (^{3}H)DOMA were present.

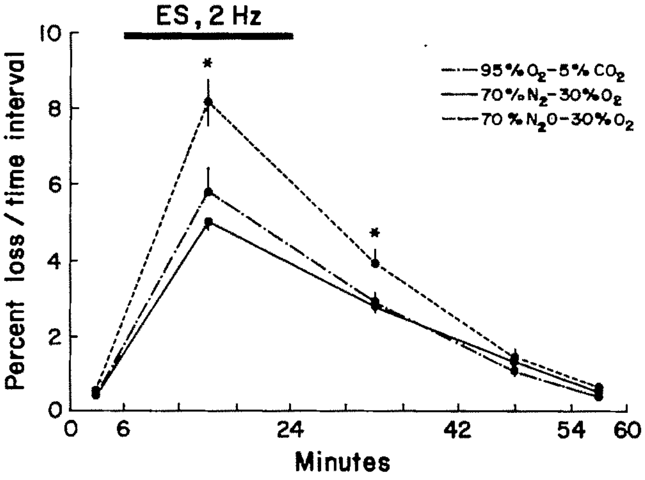

Figure 1. Effects of mixtures of nitrous oxide–oxygen, nitrogen–oxygen, and oxygen–carbon dioxide on the fractional loss over time of radiolabeled compounds from strips of dog pulmonary artery prelabeled with (^{3}H)NE. Electrical stimulation (ES) at 2 Hz was applied between the sixth and twenty-forth minutes. Means ± SE, arteries from five dogs. $^*P < 0.05$ for difference from artery exposed to 95% oxygen–5% carbon dioxide.

Under resting conditions preceding electrical stimulation, the superfusates from arteries studied in oxygen and carbon dioxide or nitrogen and oxygen did not differ in the amounts of (^{3}H)NE or in radiolabeled metabolites of NE. The superfusate from arteries studied in nitrous oxide–oxygen contained a small but significantly greater amount of (^{3}H)NE than the superfusates from the group of arteries studied in oxygen–carbon dioxide or in a mixture of nitrogen and oxygen. During resting conditions, the production of metabolites of NE was not altered significantly by nitrous oxide.

The Efflux of (^{3}H)NE and the Metabolites of (^{3}H)NE during Electrical Stimulation of Tissues in the Presence of Oxygen–Carbon Dioxide, Nitrogen–Oxygen, or Nitrous Oxide–Oxygen

The overflow of total radioactivity, (^{3}H)NE, and the metabolites of NE increased markedly with electrical stimulation in all arteries (Fig. 2). In the group of arteries studied in nitrous oxide–oxygen, overflow of (^{3}H)NE was significantly greater than in the control groups studied in oxygen–carbon dioxide or in a combination of nitrogen–oxygen. Overflow of (^{3}H)OMDA was greater in tissues exposed to nitrous oxide than in tissues exposed to either oxygen–carbon dioxide or nitrogen–oxygen. The metabolite (^{3}H)DOMA was produced in increased amounts in the presence of nitrous oxide as compared to its production in the group of arteries exposed to oxygen–carbon dioxide.

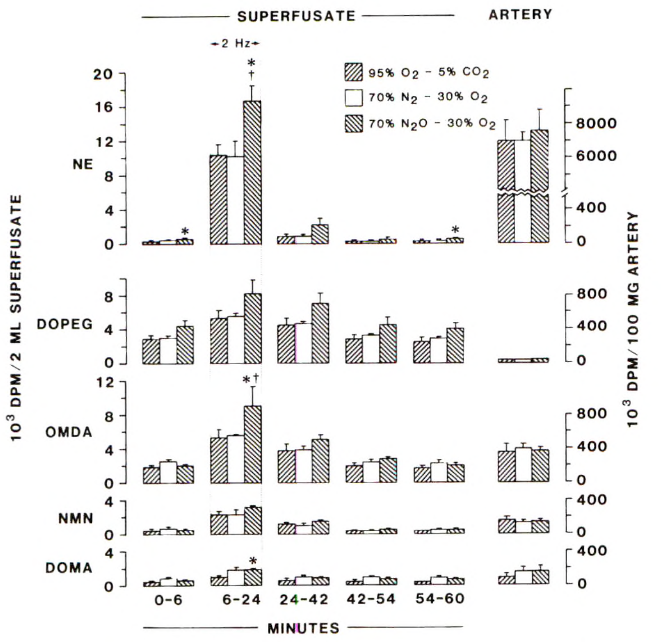

Figure 2. Changes in the efflux of (^{3}H)NE and its metabolites before, during, and after electrical stimulation (ES) at 2 Hz of strips of dog pulmonary artery superfused with Krebs–Ringer solution and aerated with 95% oxygen–5% carbon dioxide or 70% nitrogen–30% oxygen or 70% nitrous oxide–30% oxygen. Electrical stimulation was applied between the sixth and twenty-fourth minutes. Values for superfusate shown on left side of figure; those for tissues after completion of superfusion on right of figure. NE, norepinephrine; DOPEG, 3,4-dihydroxyphenylglycol; OMDA, a mixture of 3-methoxy-4-hydroxyphenylglycol and 3-methoxy-4-hydroxymandelic acid; NMN, normetanephrine; DOMA, 3,4-dihydroxymandelic acid. Values are means ± SE; arteries were taken from five dogs. * $P < 0.05$ for differences from comparable time intervals of 95% oxygen–5% carbon dioxide group; † $P < 0.05$ for significant difference from 70% nitrogen–30% oxygen group.

In the superfusate samples collected after the discontinuation of electrical stimulation, changes in the levels of (^{3}H)NE or NE metabolites were detected only in the arteries studied in the presence of nitrous oxide–oxygen where the (^{3}H)NE in superfusate was greater than in the arteries studied in the presence of oxygen–carbon dioxide.

Among the three groups of vessels studied, no significant differences were noted in the levels of (^{3}H)NE and its metabolites remaining in the tissue at the end of superfusion (Fig. 2).

Contractile Tensions Developing in Response to Electrical Stimulation of Pulmonary Artery in the Presence of Oxygen–Carbon Dioxide, Nitrogen–Oxygen, Nitrous Oxide–Oxygen

The mean maximum contractile tensions (±SE) during electrical stimulation were as follows: 0.97 ± 0.12 g/100 mg in arteries aerated with oxygen–carbon dioxide, 1.33 ± 0.40 g/100 mg in arteries aerated with nitrogen–oxygen, and 1.36 ± 0.28 g/100 mg in arteries aerated with nitrous oxide–oxygen, (n = 5 tissues/group). These differences were not statistically significant.

Discussion

In the presence of nitrous oxide, the increased amount of NE measured in the superfusate of isolated segments of dog pulmonary artery under resting conditions and during electrical stimulation of nerve endings could result from any of several possible actions by nitrous oxide. Such actions include increased release of NE, reduced uptake of NE from the synaptic cleft into nerve endings (neuronal uptake) or into extraneuronal tissues [smooth muscle and endothelial cells (extraneuronal uptake)], impaired vesicular storage of NE after NE synthesis or neuronal uptake, or impaired enzymatic breakdown of NE after uptake of NE into nerves or extraneuronal tissues.

That the cause of the increased NE in the superfusate was increased release from the nerve ending is supported by both the data showing a nitrous oxide-induced increase in fractional release of NE and the data on disposition of NE obtained by fractionating the radioactivity into NE and the metabolites of NE using column chromatography. In these latter studies, the presence of DOPEG, the metabolite of NE produced intraneuronally (17), in an amount at least equal to that produced in controls indicates that the increased overflow of NE caused by nitrous oxide was not the result of blockade of neuronal uptake of NE or of impaired intraneuronal metabolism of NE. Similarly, the presence of metabolites of NE of extraneuronal origin (OMDA, NMN and DOMA) (17) in amounts at least equal to the amounts of these metabolites produced in controls indicates that the extraneuronal uptake and subsequent metabolism of NE was not affected by nitrous oxide. Because the proportions of the metabolites of NE were not changed during exposure to nitrous oxide, the statistically increased amounts of OMDA and DOMA and the increased, albeit not statistically significant, amounts of NMN and DOPEG are likely a consequence of the increased amounts of NE that were available in the synaptic cleft to be taken up by the uptake processes. Thus it appears that nitrous oxide increases the release of NE from the nerve endings but has little effect on the processes that clear NE from the synaptic cleft or on the enzymes that degrade NE after its uptake. If this action is widespread throughout the vasculature, it might be the factor underlying the increase in urine and plasma catecholamines and the clinical signs of activation of the sympathetic nervous system that have been reported to be associated with the use of nitrous oxide (9–12).

Our studies did not allow us to determine the mechanism by which nitrous oxide causes release of NE from the nerve ending. Previous studies have indicated that hypoxia increases the release of NE (18–19) in addition to decreasing the metabolism of the released NE (18). We do not believe hypoxia can explain the present findings because the oxygen tension in the tissues exposed to nitrous oxide–oxygen was not different from the oxygen tension in the tissues exposed to nitrogen–oxygen, although the oxygen tensions of both of these groups were below the oxygen tension of tissues exposed to oxygen–carbon dioxide.

When NE was released from similar segments of dog pulmonary artery by 2 Hz stimulation and the concentration of NE in the synaptic cleft was increased by blockade of neuronal and extraneuronal uptakes, increased contractile response was seen (20). Furthermore, increasing concentrations of exogenous NE or increasing frequencies of stimulation result in dose/frequency-dependent increases in contractile responses (21–23). Thus in the present studies we would have expected the increased NE release to produce increased contractile responses. The failure to detect a significant increase in contractile tension concomitant to the increase in NE measured in the superfusate is, therefore, puzzling. It is important to note that 2 Hz stimulation does not produce a maximal contraction in this preparation, thus additional NE in the synaptic cleft should theoretically enhance the contractile response of the vessel segments. However, it is possible that the background muscular tone caused by 2 Hz stimulation of isolated segments of pulmonary artery exceeds the tone present in in vivo pulmonary artery so that the same nitrous oxide-induced increase in NE more consistently produces vasoconstriction in vivo than in the in vitro segments studied here.

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ANESTH ANALG
1986;65:565–74

Cardiovascular and Cerebrovascular Effects of Isoflurane-Induced Hypotension in the Baboon

Hugo Van Aken, Dr med, William Fitch, PhD, FFARCS, David I. Graham, PhD, FRCPath, Thomas Brüssel, Dr med, and Hermann Themann, PhD

VAN AKEN H, FITCH W, GRAHAM DI, BRÜSSEL T, THEMANN H. Cardiovascular and cerebrovascular effects of isoflurane-induced hypotension in the baboon. Anesth Analg 1986;65:565–74.

Mean arterial pressure (MAP) decreased by 10, 20, 40, and 50% of its baseline value in six anesthetized baboons with the administration of increasing concentrations of isoflurane. Mean arterial pressure, right atrial pressure, pulmonary artery pressures, and cardiac output were measured at each decrement in arterial pressure, and after the withdrawal of the isoflurane. At the same times, cerebral blood flow, the cerebral metabolic rate for oxygen, and the cerebral metabolic rate for glucose were determined. Cerebrovascular reactivity was assessed before, during, and after the administration of isoflurane, and morphologic evidence of ischemic cell change was sought at the end of the investigation. Isoflurane produced dose-related decreases in systemic vascular resistance and MAP; heart rate, cardiac output, and stroke volume did not change significantly. Although cerebral metabolism was depressed in a dose-related manner, the response of the cerebral blood flow (CBF) was biphasic. At low isoflurane concentrations, CBF decreased significantly and then increased to reach baseline values at the highest concentration. Cerebrovascular reactivity was intact at baseline and at the 20% decrement in MAP; it was impaired at the 50% decrease in MAP and when studied 100 min after the withdrawal of isoflurane. There was no morphologic evidence of ischemic cell damage in any animal.

Key Words: ANESTHETICS, VOLATILE—isoflurane. ANESTHETIC TECHNIQUES—hypotensive. BRAIN—blood flow.

Although the administration of isoflurane, like that of halothane and enflurane, produces a decrease in cerebrovascular resistance, quantitative differences appear to exist among the three drugs. At equal MAC concentrations, the vasodilatotory effects of isoflurane are less marked than those of the other two agents (1,2). Consequently, isoflurane has been considered appropriate for use during neurosurgical procedures, and recent studies have described its use in patients with intracranial aneurysms (3) or intracranial space-occupying lesions (4,5). However, the fact that isoflurane does directly affect the smooth muscle of the cerebral blood vessels suggests that, like other direct-acting vasodilators such as halothane (6), sodium nitroprusside (7), nitroglycerine (8) or adenosine triphosphate (9), it could affect the normal physiologic relationship between blood flow and arterial pressure within the cerebral circulation. The present study was undertaken to evaluate, in the subhuman primate, the systemic and cerebrovascular responses to the administration of increasing inspired concentrations of isoflurane as a hypotensive agent and to consider, in particular, its effect on cerebrovascular reactivity.

Methods

Because the basic methods employed in this study have been described in detail previously (9), only those features considered essential to an understanding of this particular study will be included here. After tranquillization (phencyclidine, 12 mg intramuscularly), anesthesia was induced in six young adult baboons with thiopental, 7.5 mg/kg intravenously, and then maintained subsequently with 70% nitrous oxide in oxygen supplemented with phencyclidine (0.15 $mg\cdot kg^{-1}\cdot min^{-1}$ intravenously). Succinylcholine (50 mg intramuscularly) was administered every 30 min to

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Address correspondence to Dr. Van Aken, Klinik für Anästhesiologie und Operative Intensivmedizin der Westfälischen Wilhelms-Universität, Albert-Schweitzer-Straße 33, D-4400 Münster, West Germany.

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provide neuromuscular blockade. The trachea was intubated and ventilation adjusted, if necessary, to provide carbon dioxide tension between 38 and 42 mm Hg, as assessed by the continuous measurement of end-tidal carbon dioxide concentration and the intermittent analysis of blood gas tensions.

After the placement of appropriate catheters, systemic arterial, right atrial, pulmonary arterial (5 French gauge, Edwards Laboratories), sagittal sinus, and subdural (intracranial) pressures were monitored continuously (Statham P23 ID transducers zero-referenced to the level of the external auditory meatus). Pulmonary capillary wedge pressure and cardiac output (CO) (thermodilution technique: 2 ml cold Dextrose 5% solution) were measured when indicated. Mean pressures were calculated as the diastolic pressure plus one-third of the pulse pressure, cerebral perfusion pressure (CPP) as mean arterial pressure (MAP) minus mean intracranial pressure, systemic vascular resistance (SVR) (dyn-sec-cm^{-5}) as

$$\frac{\left(\text{mean arterial pressure} - \text{mean right atrial pressure}\right) \times 80}{\text{cardiac output}}$$

and pulmonary vascular resistance (PVR) (dyn-sec-cm^{-5}) as

$$\frac{\left(\text{mean pulmonary arterial pressure} - \text{mean pulmonary capillary pressure}\right) \times 80}{\text{cardiac output}}.$$

Mean cerebral blood flow (CBF) was determined from the height/area equation (10), by monitoring the peak counts obtained and the rate of clearance of xenon^{-133}, after its injection into the internal carotid artery. Cerebrovascular resistance (CVR) (mm Hg·ml^{-1}·100 g·min) was calculated as

$$\text{CVR} = \frac{\text{CPP}}{\text{CBF}}.$$

Oxygen contents and glucose concentrations were measured in arterial and cerebral venous blood, and the cerebral metabolic rates for oxygen (CMRO$_2$) and glucose (CMRgluc) were calculated.

$$\text{CMRO}_2 = \text{CBF} \times (\text{CaO}_2 - \text{CvO}_2)$$

$$\text{CMRgluc} = \text{CBF} \times (\text{AV})\ \text{Dgluc}.$$

Once stable baseline values had been achieved, MAP was decreased stepwise to 90, 80, 60, and 50% of its baseline value in each animal by the administration of increasing concentrations of isoflurane (calibrated Tec vaporiser, Cyprane). Each decrement in pressure was maintained for approximately 45 min, during which time CBF was measured, cardiac output determined, the relevant hemodynamic variables recorded and the appropriate samples of arterial and cerebral venous blood obtained. After the discontinuation of the administration of isoflurane, these same variables were recorded at 30-min intervals until the baseline values of MAP had been regained.

Throughout each investigation, the end-tidal concentration of isoflurane was monitored continuously with an infrared analyzer (Engström, Emma) and its concentration in plasma measured intermittently based on the GLC technique (Pye 204 Chromatograph) described by Allott et al. (11). The physiologic responsiveness of the cerebral circulation was assessed by noting the change (if any) in CBF, produced by an acute increase in MAP of around 20 mm Hg (induced by the intravenous administration of angiotensine II amide (Ciba)), before the addition of the isoflurane to the inspired gas mixture, at the 20% decrease in MAP, at the 50% decrease in MAP, and at 100 min after the withdrawal of the isoflurane. Systemic administration of angiotensin itself has no effect on CBF (12).

At the end of the procedure the animals were placed supine, and after heparinization (100 IU/kg) a thoracotomy was performed. Biopsies of ventricular muscle were taken for electron microscopy, and after perfusion fixation (13) the brain was subjected to a full neuropathologic examination. The biopsies of ventricular muscle were fixed in 3.5% glutaraldehyde (2 hr at 4°C). After rinsing in phosphate buffer, fixation was continued in 1.33% OsO$_4$ for another 2 hr. After dehydration in graded concentrations of alcohol, the tissue was embedded in Epon 812 and the sections stained with uranyl-acetate and lead citrate.

Mean values and standard deviations were calculated for each variable, and the effects associated with each alteration in MAP were compared (Friedman test). $P \leq 0.05$ was considered significant.

Results

Cardiovascular Variables

Changes in the systemic circulation observed during and after the administration of isoflurane are summarized in Table 1. The required stepwise decreases in MAP were achieved easily by the administration of increasing concentrations of isoflurane: MAP decreasing from its baseline value of 103 mm Hg (± 14) to 93 mm Hg (± 13), 82 mm Hg (± 11), 62 mm Hg (± 8) and 53 mm Hg (± 6) as the end-expired concentration of isoflurane increased from 0 to 0.24% (± 0.18), 0.5% (± 0.35), 0.95% (± 0.7), 1.4% (± 1.0).

Once the desired level of hypotension had been achieved, only minimal adjustments of the inspired concentration were necessary to maintain this value for the subsequent 45 min. After the withdrawal of

Table 1. Changes in Systemic Hemodynamic Variables during and after Hypotension Induced with Increasing Concentrations of Isoflurane[a]

						Time (min) after isoflurane		
						30	60	85
Reduction in MAP (% of control)	0	10.5 ± 0.9	21 ± 1.9	40 ± 1.8	49 ± 1.7	9.6 ± 6.4	0.12 ± 8.8	2.26 ± 9.9
End-expired concentration of isoflurane (vol%)	0	0.24 ± 0.18	0.5 ± 0.35	0.95 ± 0.7	1.4 ± 1.0	0.05 ± 0.08	0	0
MAP (mm Hg)	103 ± 14	93 ± 13	82 ± 11	62^b ± 8	53^b ± 6	93 ± 12	103 ± 13	105 ± 14
$\overline{\text{PA}}$ (mm Hg)	16.2 ± 4.1	15.5 ± 4.1	14.5 ± 4.1	15.3 ± 3.0	14.7 ± 3.6	17.1 ± 2.9	17.5 ± 3.8	17.4 ± 3.7
$\overline{\text{RAP}}$ (mm Hg)	4.2 ± 1.2	4.3 ± 1.4	4.3 ± 1.4	4.5 ± 1.4	5.3 ± 1.8	5.2 ± 1.7	4.8 ± 1.7	4.8 ± 1.7
$\overline{\text{PCWP}}$ (mm Hg)	4.8 ± 2.1	4.3 ± 1.8	4.6 ± 1.9	5.2 ± 1.5	5.2 ± 1.6	6 ± 1.3	5.3 ± 0.8	5.7 ± 1.2
Cardiac output (L/min)	1.4 ± 0.3	1.4 ± 0.3	1.4 ± 0.3	1.3 ± 0.2	1.4 ± 0.4	1.6 ± 0.5	1.6 ± 0.4	1.6 ± 0.4
Heart rate (beats/min)	109 ± 21	113 ± 21	113 ± 19	112 ± 17	111 ± 16	126 ± 12	120 ± 13	120 ± 14
Stroke volume (ml/beat)	13 ± 2	13 ± 1	12 ± 1	12 ± 2	13 ± 4	12 ± 3	13 ± 2	13 ± 3
SVR (dyn-sec-cm^{-5})	5765 ± 1168	5120 ± 1259	4739 ± 1159	3532^b ± 810	2781^b ± 672	4690 ± 1320	5029 ± 1015	5159 ± 837
PVR (dyn-sec-cm^{-5})	664 ± 209	646 ± 230	599 ± 230	622 ± 176	562 ± 251	581 ± 176	626 ± 230	609 ± 240

Abbreviations: MAP, mean systemic arterial pressure; $\overline{\text{PA}}$, mean pulmonary arterial pressure; $\overline{\text{RAP}}$, mean right atrial pressure; $\overline{\text{PCWP}}$, mean pulmonary capillary wedge pressure; SVR, calculated systemic vascular resistance; PVR, calculated pulmonary vascular resistance.

[a] ($n = 6$), mean ± SD.

[b] $P \leq 0.05$.

Table 2. Changes in Cerebrovascular Variables during and after Hypotension Induced with Increasing Concentrations of Isoflurane[a]

						Time (min) after isoflurane		
						30	60	85
Reduction in MAP (% of control)	0	10.5 ± 0.9	21 ± 1.9	40 ± 1.8	49 ± 1.7	9.6 ± 6.4	0.12 ± 8.8	2.26 ± 9.9
End-expired concentration of isoflurane (vol %)	0	0.24 ± 0.18	0.5 ± 0.35	0.95 ± 0.7	1.4 ± 1.0	0.05 ± 0.08	0	0
Cerebral blood flow (ml·min^{-1}·100g^{-1})	48.3 ± 3.5	40.7 ± 2.7	34.7^b ± 4.0	38.3 ± 4.8	45.7 ± 5.5	58.3 ± 11.8	55.3 ± 8.8	51.8 ± 5.2
$CMRO_2$ (mlO$_2$·min^{-1}·100 g^{-1})	3.64 ± 1	2.86 ± 0.9	2.56 ± 0.6	1.78^b ± 0.8	1.98^b ± 0.4	2.46 ± 0.6	2.72 ± 0.6	2.95 ± 0.7
CMRgluc (mg·min^{-1}·100g^{-1})	24.42 ± 6.53	18.04 ± 4.32	19.40 ± 10.09	11.72^b ± 6.11	13.02^b ± 6.87	31.08 ± 9.97	29.42 ± 9.92	25.02 ± 13.41
Intracranial pressure (mm Hg)	10.7 ± 3.3	10.0 ± 2.9	10.5 ± 3.3	10.8 ± 3.7	11.2 ± 4.4	10.5 ± 3.1	11.0 ± 3.2	11.3 ± 3.3
SSVP (mm Hg)	8.5 ± 2.2	8.2 ± 2.6	7.7 ± 3.0	8.5 ± 2.3	10.5 ± 4.0	11.5 ± 2.9	11.5 ± 3.3	11.0 ± 2.9
CPP (mm Hg)	92.6 ± 12	82.5 ± 12	71.1 ± 9.7	50.7^b ± 5	41.6^b ± 6.3	82.6 ± 11.2	91.8 ± 11.3	93.9 ± 13.4
CVR (mm Hg·ml^{-1}·100g·min)	1.92 ± 0.26	2.04 ± 0.37	2.07 ± 0.35	1.35 ± 0.30	0.94^b ± 0.28	1.55 ± 0.33	1.70 ± 0.4	1.83 ± 0.33

Abbreviations: $CMRO_2$, cerebral metabolic rate for oxygen; CMRgluc, cerebral metabolic rate for glucose; SSVP, superior sagittal sinus venous pressure; CCP, cerebral perfusion pressure; CVR, cerebral vascular resistance.

[a] $n = 6$, mean ± SD.

[b] $P \leq 0.05$.

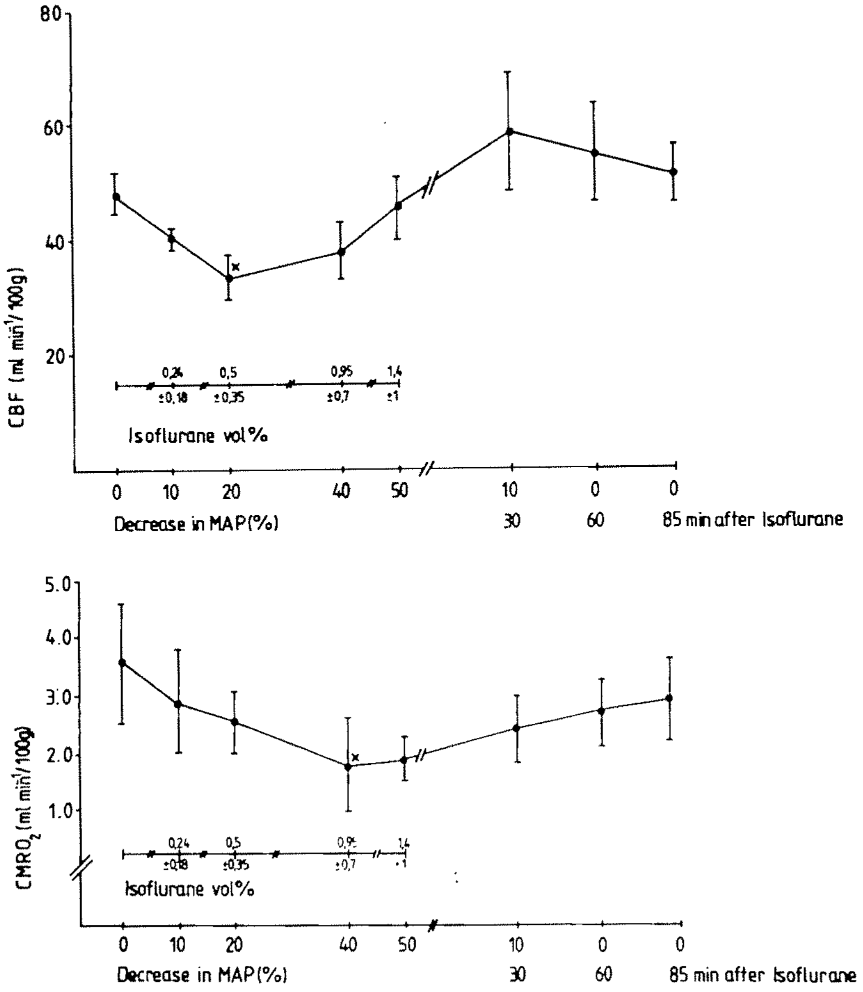

Figure 1. Cerebral blood flow (CBF) and cerebral metabolic rate for oxygen (CMRO$_2$) at different levels of hypotension during increasing concentrations of isoflurane, and 85 min after the withdrawal of isoflurane. Mean values ± SD ($n = 6$). X indicates $P \leq 0.05$.

isoflurane, MAP increased slowly, and baseline values were attained fully after 60 min. There was no evidence of rebound hypertension. The decrease in MAP was due entirely to a dose-dependent and significant decrease in SVR, because cardiac output (CO) did not change. Heart rate and stroke volume remained close to their baseline values, and there were no significant changes in pulmonary artery, right atrial or pulmonary capillary wedge pressures.

Cerebrovascular Variables

Decrease in mean arterial pressure (Table 2). Initially, as MAP was decreased moderately (21 ± 2%) by low concentrations of isoflurane (0.5 ± 0.35 vol%), mean CBF decreased from 48 ± 4 ml·min^{-1}·100 g^{-1} to 35 ± 4 ml·min^{-1}·100 g^{-1} (28 ± 6%) ($P \leq 0.05$). This decrease was in line with the induced decreases in the cerebral metabolic rate for oxygen—from 3.64 ± 1 ml O$_2$·min^{-1}·100 g^{-1} to 2.56 ± 0.6 ml O$_2$·min^{-1}·100 g^{-1} ($P > 0.05$).

At the two most marked decreases in MAP (40 ± 2% and 49 ± 2%), and in association with the two highest concentrations of isoflurane (0.95 ± 0.7 vol% and 1.4 ± 1 vol%), CBF increased (38 ± 5 ml·min^{-1}·100 g^{-1}; 46 ± 6 ml·min^{-1}·100 g^{-1}) but did not exceed its initial control value. On the other hand, CMRO$_2$ continued to decrease, reaching 1.78 ± 0.8 ml O$_2$·min^{-1}·100 g^{-1} ($P \leq 0.05$) as the isoflurane concentration increased. After the withdrawal of the isoflurane, and in association with the resultant increase in MAP, CBF increased to above its baseline value, an increase that was at its highest (58 ± 12 ml·min^{-1}·100 g^{-1}) 30 min after the discontinuation of the isoflurane. However, because of the variability between the individual animals, this increase was not significant ($P > 0.05$) (Fig. 1). Eighty-five minutes after the withdrawal of isoflurane, CBF had returned to its baseline value (MAP 105 mm Hg ± 14). Because there were no significant changes in intracranial pressure (ICP) and sagittal sinus venous pressure (SSVP) ($P > 0.05$), decreases in CPP could only be due to the decreases in MAP.

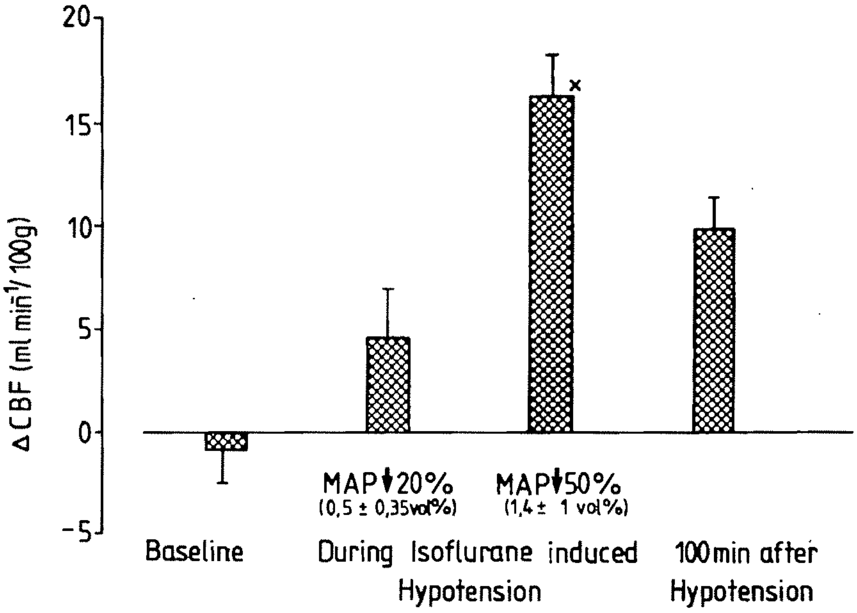

Figure 2. Changes in CBF (Δ CBF) during acute increase in systemic arterial pressure produced by intravenous administration of angiotensine II before, during, and after administration of isoflurane.

Δ CBF is the difference in CBF before and during an acute increase in MAP of approximately 20 mm Hg.

When the cerebral autoregulation is intact, this increase in MAP does not change CBF.

Autoregulation was intact before and during the lower concentration of isoflurane at the 20% decrement in MAP, but it was impaired significantly by the time MAP had been decreased to 50% of baseline by higher concentrations of isoflurane. Even 100 min after withdrawal of isoflurane, changes in CBF were elevated but not significant.

Mean values ± SD. X indicates $P \leq 0.05$.

Acute increases in mean arterial pressure (Fig. 2, Table 3). Because CBF did not differ significantly from its baseline value, when MAP was increased acutely (by approximately 20 mm Hg) before the administration of the isoflurane, or at the 20% decrease in MAP, it can be assumed that the cerebral vessels were responding in a physiologic manner to the acute alterations in systemic arterial pressure. However, at the 50% decrease in MAP, similar acute increases in MAP were accompanied by marked increases in CBF ($P \leq 0.05$) and these were present also in four of the animals 100 min after the withdrawal of isoflurane.

Isoflurane Concentrations

End-tidal concentrations of isoflurane and plasma isoflurane concentrations at the different levels of MAP are summarized in Table 4.

Neuropathology

Macroscopic observations. The brains of all animals appeared normal externally. After slicing, the brains of all six animals appeared uniformly blanched, indicating that perfusion had been satisfactory. There was no evidence of brain swelling, and internal herniations were not seen. Small areas of hemorrhage were seen in the brain slices of three animals in areas adjacent to the tip of the subdural catheter.

Microscopic observations. The brains of all six animals showed histologic evidence of good tissue fixation. The cytologic artifacts, the "dark cell" and "hydropic cell" were not seen (14,15). In three animals there was histologic evidence of focal ischemic brain damage of the type described previously in FAM-fixed material (15,16). In two of these animals, the ischemic damage was associated predominantly with hemorrhage due to catheterization. In addition, however, there were two animals in which focal ischemic damage was present in the striatum.

In none of the animals was there evidence of diffuse hypoxic brain damage or of ischemic damage in the selectively vulnerable areas. In none of the animals was there histologic evidence of raised intracranial pressure (17).

The pattern of abnormalities (hemorrhage and ischemic necrosis) suggests that it can all be accounted for by operative procedures. If this is correct as far as the first three animals are concerned, then the brains of all six animals can be considered normal, i.e., there is *no* histologic evidence of hypoxic damage.

Electron microscopy of heart muscle (Fig. 3). The organization of cristae mitochondriales appeared normal and, in comparison with normal heart muscle tissue, the number of cristae mitochondriales was not reduced. There was no evidence of any alteration in the heart muscle cells. The organization of the heart myofibrils was normal.

Discussion

Rapid and dose-related decreases in systemic arterial pressure were produced readily by the administration of increasing concentrations of isoflurane, and were

Table 3. Changes in CBF in the Individual Baboon during Acute Increases in Systemic Arterial Pressure

	Isoflurane-induced hypotension (changes in CBF, $\text{ml}\cdot\text{min}^{-1}\cdot100\text{g}^{-1}$)			
		During		
Number of baboons	Before	↓ 20% MAP	↓ 50% MAP	After
1	−8	3	16	14
2	3	9	17	6
3	2	12	25	10
4	−5	0	16	5
5	3	5	14	12
6	0	2	10	13
Mean ± SD	−0.83 ± 4.62	4.5 ± 5.32	16.33 ± 4.92[a]	10 ± 3.74

Acute increases in pressure were induced by the administration of angiotensine II amide before the administration of isoflurane (MAP + 22 ± 6 mm Hg), during the administration of low concentrations of isoflurane once MAP had been decreased approximately 20% of control (19 ± 1 mm Hg), during higher concentrations of isoflurane once MAP had been decreased 50% of control (20 ± 2 mm Hg), and again 100 min after discontinuing the isoflurane once CBF had returned to control value (21 ± 3 mm Hg).

[a] Individual, mean values, and SD; $P \leq 0.05$.

Table 4. Plasma Isoflurane Concentrations[a]

Decrease in MAP (%)	Plasma–isoflurane concentration (mg/100 ml)	End-tidal concentration of isoflurane (vol %)
0 (baseline)	ND	0
10	0.33 ± 0.2	0.24 ± 0.18
20	1.36 ± 0.48	0.5 ± 0.35
40	2.48 ± 0.61	0.95 ± 0.7
50	3.64 ± 0.47	1.4 ± 1.0
10% after withdrawal of isoflurane	0.57 ± 0.12	0.05 ± 0.08
Baseline	0.27 ± 0.16	0
Baseline	ND	0

[a] Mean ± SD. ND, not detected.

maintained easily by minor adjustments of inspired concentration. After the withdrawal of the isoflurane, the arterial pressure returned steadily towards its baseline value; there was no evidence of rebound hypertension.

Because nitrous oxide, succinylcholine, and phencyclidine were given during the entire experiment, we cannot totally discount the possibility of some influence of these agents on systemic and cerebrovascular hemodynamics. However, because the baseline measurements and all measurements during and after withdrawal of isoflurane were obtained under similar anesthetic conditions, it seems likely that the observed changes can be ascribed to isoflurane. Previously, investigations revealed that the basic anesthetic technique (N_2O and phencyclidine) does not influence the cerebral circulation (6, 18).

General Cardiovascular Considerations

The isoflurane-induced decreases in MAP were due to systemic vasodilation, as reflected in the progressive decreases in SVR. Neither CO nor stroke volume changed significantly, even with the highest of the concentrations administered. Although, like the other commonly-used volatile anesthetic agents, isoflurane decreases myocardial contractility in vitro (19), a number of in vivo studies in volunteers (20) and patients (2,21) support the belief that concentrations of isoflurane up to 2 × MAC have little effect on CO. However, one must also consider the possibility of there being some depression in vivo of the myocardium by isoflurane because CO did not increase despite a decrease in afterload and an unchanged preload (22).

It is argued that this maintenance of CO is due to an associated increase in heart rate (23,24) that compensates for small decreases in stroke volume. In the present study there were no significant changes in either of these variables. It may be that the stability of heart rate can be explained by the provision of neuromuscular blockade, the preoperative tranquilization, the basic technique of anesthesia, or the age of the animals (25,26). Whatever the mechanism, lack of a reflex tachycardia during the period of isoflurane-induced hypotension was notable.

Despite the rather prolonged duration of hypotension (approximately 3.5 hr), no abnormalities could be detected by electron microscopy in the ultrastructure of the myocardial cells. This is similar to the findings after hypotension induced with nitroglycerin but is in sharp contrast to those observed in association with nitroprusside-induced hypotension of similar degree and duration (27).

Cerebrovascular Considerations

The most striking effect of isoflurane on the cerebral circulation was the biphasic pattern of the changes in cerebrovascular resistance: the lower concentrations inducing vasoconstriction, the two higher concentra-

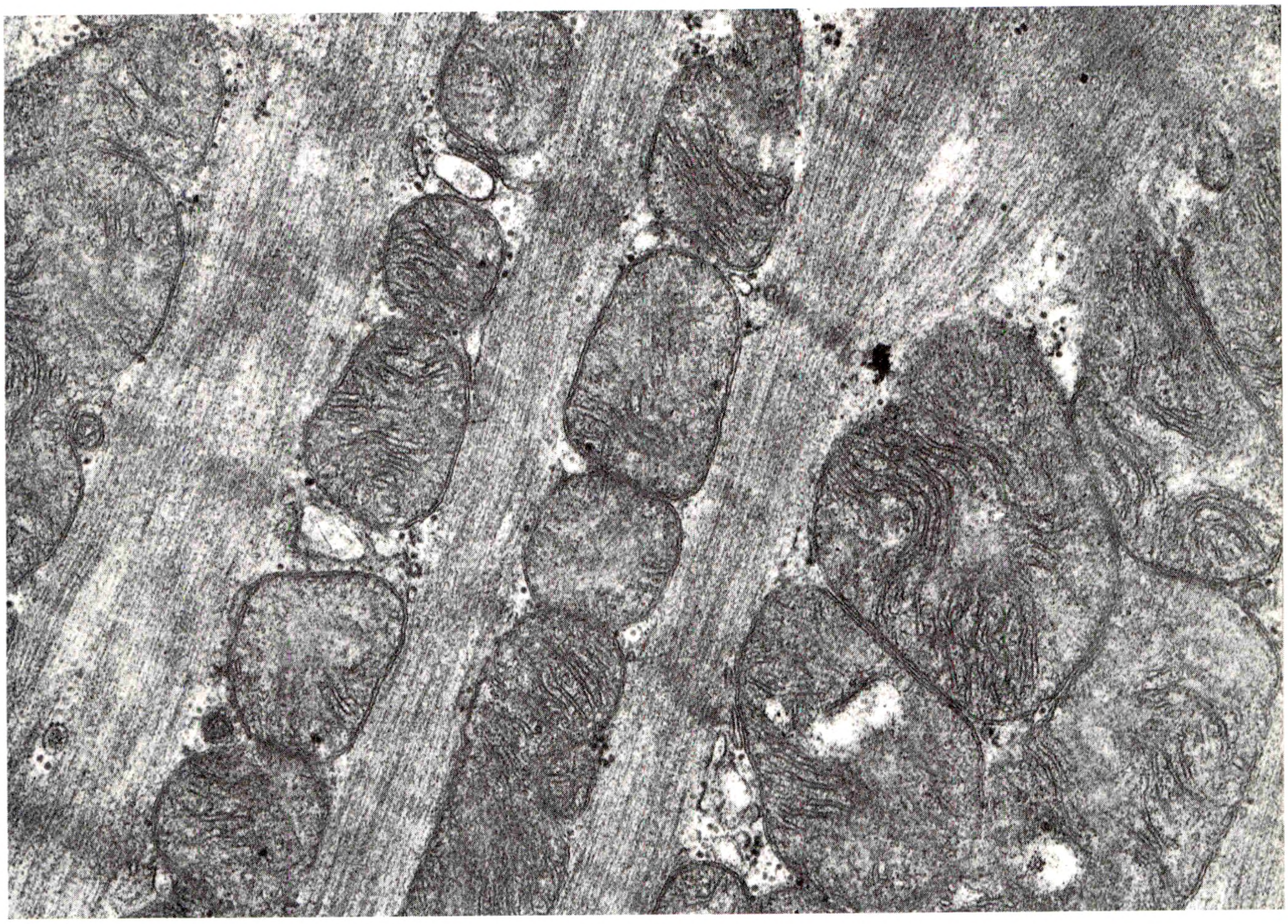

Figure 3. Electronmicroscopic picture of heart muscle cell after isoflurane-induced hypotension (1/48,400). There is no evidence of alteration of the heart muscle cells. There are no signs of hypoxic damage.

tions associated with vasodilatation. Like halothane and enflurane, isoflurane decreases the oxygen consumption of the brain (28–31). This characteristic of isoflurane was confirmed in the present study; and, as a result, the initial decreases in cerebral blood flow can be understood readily. A smaller supply is adequate to meet the lower demand for oxygen. Under these circumstances, the normal coupling between flow and metabolism was evident. This is in contrast to halothane, where even at low concentrations (0.5 vol%), CBF increases whereas $CMRO_2$ decreases (32). Also in evidence during the first phase (isoflurane concentrations approximately 0.5–1 × MAC) was the physiologic nature of the relationship between cerebral blood flow and perfusion pressure. Blood flow did not change significantly from baseline despite the acute increase in MAP. This unaffected autoregulation during 1 MAC isoflurane anesthesia could not be observed during equal levels of halothane and enflurane. However, during 0.5 MAC, none of the three agents alter cerebral autoregulation (33). The observation of a significant decrease in CBF at the lowest concentrations of isoflurane is quite different from those obtained previously when other "hypotensive" agents—halothane, sodium nitroprusside, nitroglycerin, adenosine triphosphate—were studied in a similar animal model (6,8,9). Although there was a suggestion that CBF might be less than baseline during the administration of low concentrations of halothane the change did not reach statistical significance (6). The most marked changes, however, were associated with the administration of low doses of the other two drugs. In the animals receiving sodium nitroprusside, CBF had increased by 16% at an MAP of 85 ± 2 mm Hg, and in those receiving nitroglycerin the increase in CBF was 40% at a similar MAP value (8).

As the inspired concentration of isoflurane was increased further, to achieve the 40% and 50% decrements in MAP, the cerebral metabolic demand for oxygen decreased to a value roughly 50% of its baseline value at an end-expiratory isoflurane concentration of 0.95 ± 0.7%. There was no further significant change at the highest concentration. Cerebral blood flow, on the other hand, increased to reach a mean value (at an MAP of 53 ± 6 mm Hg) not significantly different from baseline. From the arguments put forward earlier, it will be obvious that in this second phase there was an uncoupling of the relationship between flow and metabolism: the direct vasodilator actions of the higher concentrations of isoflurane predominating over the effects of the decrease in oxygen demand. Whether CBF would have increased further had we continued to increase the concentration of isoflurane cannot, of course, be defined from this study. However, because CBF was pressure passive in this second phase, (Fig. 2), any further increase would seem unlikely. The effects of the consequent decrease in arterial pressure predominate over any additional dilator effect of higher concentrations of isoflurane. However, this consideration allows us to explain some of the differences (and some of the similarities) between the findings of other workers and our own because it seems likely that at concentrations greater than about 2 × MAC isoflurane, the absolute value of CBF is more dependent on arterial pressure than on the isoflurane concentration. For example, the small increases in CBF reported by Cucchiara et al. (29) can be explained by the slightly higher value of MAP obtained in that study during the administration of isoflurane, 1.4%. Likewise, in the study by Murphy et al. (1), the observed increases in CBF are perfectly understandable when one appreciates that systemic arterial pressure was maintained close to its baseline value throughout the administration of the increasing concentrations of isoflurane in that investigation. It is more difficult to reconcile the marked decrease in CBF (60%) noted by Newberg et al. (34) in association with an isoflurane-induced decrease in MAP to 50 mm Hg. Interestingly enough, however, the absolute value of CBF obtained by Newberg et al. at an MAP of 50 mm Hg (49 ± 6 $\mathrm{ml{\cdot}min^{-1}{\cdot}100\ g^{-1}}$) was almost identical with the value obtained in the present study (46 ± 6 $\mathrm{ml{\cdot}min^{-1}{\cdot}100\ g^{-1}}$) at an MAP of 53 ± 6 mm Hg. One is left with the impression that the baseline conditions must have differed between their study and ours. Certainly, the anesthetic techniques were different, and it could be argued that the animals studied by Newberg et al. were in a hyperdynamic circulatory state at the start of investigation with unusually high values for cardiac index (3.20 ± 0.26 $\mathrm{L{\cdot}min^{-1}{\cdot}m^{-2}}$) and CBF (122 ± 20 $\mathrm{ml{\cdot}min^{-1}{\cdot}100\ g^{-1}}$).

In the present study the highest values of CBF (and SSVP) were obtained in the period after the discontinuation of the administration of the isoflurane. Unfortunately, the variability in CBF among the animals was such that no significant differences emerged. Thus it would be wrong to place too much emphasis on these changes. Nevertheless, it does appear likely that the mechanism behind the increases in CBF was the steady return of the MAP to its baseline value. Moreover, changes in CBF produced by an acute increase in MAP during the highest concentration of isoflurane (1.4 ± 1.0 vol%) and in four of the animals 100 min after the withdrawal of the isoflurane clearly demonstrate that the cerebral vessels were responding passively to alterations in MAP. This indicates that at this time the normal responsiveness of the cerebral circulation was impaired, and that the cerebrovascular bed was pressure passive in four of the animals after the withdrawal of isoflurane. We cannot precisely determine whether the alteration in reactivity at this point in the investigation was the result of the effect of isoflurane on cerebrovascular smooth muscle, of local tissue acidosis from an inadequate oxygen supply, or of a combination of both mechanisms. However, the first explanation seems the most likely for a number of reasons. First, as demonstrated, isoflurane depresses the cerebral requirement for oxygen and has been considered to have "protective" potential (35). Second, at no time in the investigation did CBF decrease to values that could be considered ischemic. Admittedly, the technique used in the determination of CBF was unable to measure CBF on a regional basis and, consequently, could neither demonstrate any regional nonhomogeneity in flow nor assess the absolute values of CBF in the arterial boundary zones. However, the study did demostrate that there was no morphologic evidence of ischemic cell change in these areas. Third, Michenfelder and Theye (36) were unable to demonstrate biochemical evidence of cerebral tissue hypoxia in dogs subjected to halothane-induced hypotension until MAP had been decreased to about 40 mm Hg; a decrease from baseline MAP of at least 65%. In a later, similar study, they found that under isoflurane-induced hypotension to an MAP of 40 mm Hg, cerebral energy state was normal (34). However, these arguments are not conclusive, and further studies would be required to answer the question definitively.

Glucose metabolism was not adversely affected during the administration of isoflurane; even at the lowest value of arterial pressure studied there was no evidence of anaerobic glycolysis in the brain. Systemic plasma glucose concentrations did not change throughout the investigation, showing that isoflurane per se did not increase plasma glucose concentrations. Consequently, the administration of isoflurane would be unlikely to provide additional substrate should the drug be administered in a patient with an ischemic focus (37).

Clinical Considerations

It would appear from this study that the administration of low concentrations of isoflurane (possibly the equivalent of up to 1 MAC) produces controllable decreases in MAP, a dose-related depression of cerebral metabolism, and the preservation of the physiologic relationships between flow and pressure and between flow and metabolism. With higher concentrations, the direct vasodilator effects of isoflurane predominate. CBF increases, and autoregulation is impaired (in a situation in which there was no evidence of intracranial pathology). From a practical point of view this means that when higher concentrations are administered, the cerebral blood vessels cannot adapt normally to alterations in arterial pressure, and any acute alteration in systemic arterial pressure will be reflected by directionally similar changes in flow. This need not be disadvantageous in that the anesthetist could, under such circumstances, manipulate the flow to the brain by modulation of arterial pressure.

In conclusion, we would like to make two points. First, this investigation was carried out on young adult animals with normal hearts and no evidence of intracranial pathology. All of these animals were shown to be autoregulating normally at the start of the investigation. Thus one cannot extrapolate the present finding to patients in whom autoregulation is impaired. And second, the increases in the concentrations of isoflurane (and the consequent decreases in MAP) were produced gradually, over a relatively long period of time. In the present study intracranial pressure did not change substantially at any point, presumably because the intracranial contents had both the time and the space in which to compensate. We have some evidence that this may not be the case (unpublished observations) when the isoflurane concentration is increased more rapidly.

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Pharmacokinetics of Inhaled Anesthetics in Humans:
Measurements during and after the Simultaneous Administration of Enflurane, Halothane, Isoflurane, Methoxyflurane, and Nitrous Oxide

Randall L. Carpenter, MD, Edmond I. Eger II, MD, Brynte H. Johnson, AB,
Jashvant D. Unadkat, PhD, and Lewis B. Sheiner, MD

CARPENTER RL, EGER EI II, JOHNSON BH, UNADKAT JD, SHEINER LB. Pharmacokinetics of inhaled anesthetics in humans: measurements during and after the simultaneous administration of enflurane, halothane, isoflurane, methoxyflurane, and nitrous oxide. Anesth Analg 1986;65:575–82.

To determine the relative washin and washout characteristics of isoflurane, enflurane, halothane, and methoxyflurane, we administered all four anesthetics simultaneously (total = 1.1 MAC) to nine healthy patients for 2 hr. Concentrations of anesthetics in end-tidal gases were measured during washin and for 5–9 days during washout. Multiexponential (multicompartment) models were fit to the washin and washout curves using least-squares analysis. Slowly equilibrating compartments could only be identified during washout. For 27 of the 36 data sets, five-compartment models fit the washout curves significantly better than four-compartment models. The time constant for our first compartment is consistent with that predicted for washout of the lungs. Time constants for the second, third, and fifth compartments were consistent with current data for blood flows and solubilities of vessel-rich, muscle, and fat tissue groups, respectively. The fourth compartment has a time constant that lies between the time constants predicted for muscle and fat.

Key Words: ANESTHETICS, VOLATILE—enflurane, halothane, isoflurane, methoxyflurane. METABOLISM—drug. PHARMACOKINETICS—volatile anesthetics.

Current data defining the pharmacokinetic properties of inhaled anesthetics have several limitations. First, few studies have been of sufficient duration to adequately examine the effects of distribution of anesthetics to slowly equilibrating compartments such as muscle or fat. Determination of the contributions of muscle and fat requires measurement of washin or washout for hours or days. Studies that have examined the pharmacokinetic properties of inhaled anesthetics for such durations (1,2) report data that are not completely consistent with current concepts of inhaled anesthetic pharmacokinetics. For example, Holaday et al. (2) found that time constants for washout of isoflurane from muscle and fat were 2.0 ± 0.2 and 17.4 ± 2.2 hr (mean ± SE), respectively. The time constant for muscle is more than twice that predicted using known values for solubility of isoflurane and blood flow in muscle (3,4). The time constant for fat is also inconsistent, being less than half that predicted (3,4).

Second, one study of anesthetic pharmacokinetics may be difficult to compare with another. Differences in methodology, physiologic condition of subjects, or response of subjects to different agents may compromise any such comparison. Thus, dissimilarities in the pharmacokinetic patterns found by various investigators for different anesthetics may be due to differences in ventilation, cardiac output, or distribution of blood flow in different subject populations, rather than to actual differences in the pharmacokinetic properties of the anesthetics.

Third, although a few studies have reported on anesthetics administered concurrently (5–8), they did not control for the pharmacokinetic impact of two additional variables. When trace concentrations rather than anesthetizing concentrations are applied (6,7), hepatic extraction of anesthetic may increase (9) and therefore play a greater role in elimination of anesthetic. Also, when anesthetizing concentrations were

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Address correspondence to Dr. Eger, Department of Anesthesia, University of California, Room 1386 HSE, Third and Parnassus Avenues, San Francisco, CA 94143.

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used in these studies, only pairs of volatile anesthetics, rather than the full range of those available, were administered simultaneously (5,7,8).

The present study supplies new data on the pharmacokinetics of inhaled anesthetics by measuring the pharmacokinetic characteristics of the four currently available potent inhaled agents during 2 hr of washin and 5–9 days of washout, when all four anesthetics are given simultaneously. Simultaneous administration of drugs to the same subject eliminates intersubject variability: changes in ventilation or circulation, for example, would affect the pharmacokinetics of the drugs equally. Also, the sum of the concentrations administered was equal to an anesthetizing concentration of anesthetic. The results from this study support and enlarge upon the current interpretations of the pharmacokinetics of inhaled anesthetics.

Methods

We received approval from the Committee on Human Research and informed consent to study four healthy men and five healthy women (39 ± 4 yr, mean ± SE) of average height (170 ± 2 cm) and weight (73 ± 3.7 kg) who were undergoing donor nephrectomy.

All patients were premedicated with morphine and diazepam. Anesthesia was induced with thiopental and fentanyl. Pancuronium or vecuronium was used to facilitate tracheal intubation and to maintain muscle relaxation. Patients were ventilated through a nonrebreathing circuit to keep end-tidal partial pressure of carbon dioxide at normal levels, as measured by mass spectrometry.

After normocapnia was established, the inspired gas was changed from 100% O_2 to 65–70% N_2O, balance O_2. Inspired and end-tidal concentrations of N_2O were measured by mass spectrometry. After 30 min of equilibration, the end-tidal partial pressure of N_2O was 98% of the inspired concentration. A mixture of potent inhaled anesthetics, each at 0.3 MAC, then was added to the stream of N_2O delivered to the patients. That is, isoflurane (0.348 ± 0.007%), enflurane (0.518 ± 0.012%), halothane (0.226 ± 0.005%), and methoxyflurane (0.0469 ± 0.0045%) (mean ± SE of the average concentrations administered for the nine experiments) were administered at constant inspired concentrations through a nonrebreathing system for exactly 2 hr. The average coefficient of variation of the measured inspired concentration in all experiments for all anesthetics was 0.03. To minimize the second–gas effect, we decreased the inspired concentration of N_2O by 5% (i.e., to 60–65%) as we introduced the potent inhaled agents. After 2 hr, the potent inhaled agents were discontinued, and anesthesia was maintained with fentanyl, thiopental, and 60–65% N_2O for the rest of the operation. The average total dose of fentanyl was 262 ± 65 mcg.

During the 2-hr washin period, gas samples were obtained for determination of the fractional concentration of anesthetic inspired (F_I) and the fractional concentration of anesthetic in the alveoli (F_A). F_A samples were collected at 0.25 and 0.5 min in six patients, and with each breath for the first 0.5 min in the remaining three patients. F_A samples then were collected at 0.75, 1, 1.5, 2, and 3 min. F_I and F_A samples were collected at 5, 7, 10, 15, 20, 30, 40, 50, 60, 75, 90, 105, and 120 min. For logistical reasons, F_I samples were not collected for the first 3 min. Instead, the values produced by F_I samples collected at 10, 15, and 20 min were averaged, and this value was used as the F_I for the first 3 min. F_I samples were collected proximal to the nonrebreathing valve. F_A samples were collected through a catheter placed near the tracheal end of the endotracheal tube. The endotracheal tube was connected to the nonrebreathing valve with a length of flexible Teflon® tubing having an internal volume of approximately 100 ml. Teflon® tubing was used to avoid the absorption and release of anesthetic that occurs with plastics such as polyethylene. The additional deadspace was used to guard against the contamination of end-tidal samples with inspired gas. All gas samples were collected in 50-ml glass syringes and were stored upright (i.e., with slight positive pressure) until analyzed.

Once administration of the anesthetic vapors was discontinued, we drew F_A gas samples at the same intervals used during the 120 min of washin. (The total intraoperative sampling time for the volatile agents was 214 ± 14 min.) Samples were drawn thereafter at approximately 150, 200, 350, 500, 700, 1200, 1800, and 2700 min, and then once a day for a total of 5 to 9 days. At the start of washout, the delivery tubing was changed to ensure that the inspired concentration of vapors was zero. For samples taken after the first 2–4 hr of elimination, we used fresh glass syringes to avoid using those that had contained gases at the higher concentrations of anesthetics. The sampling procedure was interrupted during washout by the completion of surgery and extubation. Samples were not collected after extubation until patients were awake enough to be cooperative. F_A samples then were collected while the patient breathed through a mouthpiece and a low resistance nonrebreathing valve. Noseclips were used to prevent breathing through the nose.

A two-column gas chromatograph (Tracor Model 550) was used to separate and detect isoflurane, enflurane, halothane, and methoxyflurane. Both col-

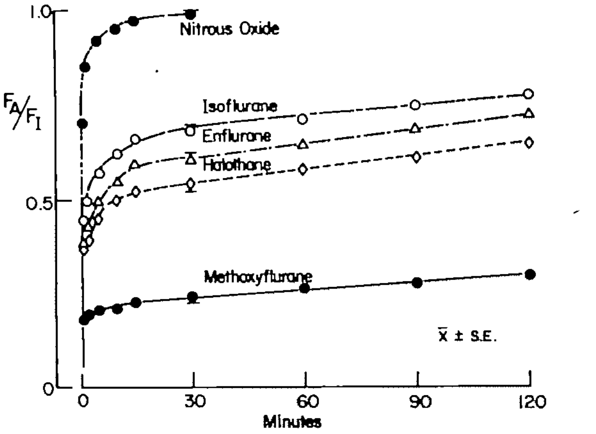

Figure 1. The rise in the ratio of the alveolar to the inspired concentrations of anesthetic (F_A/F_I) was plotted against time (means for all data ± SE for 30-min values).

umns were composed of 10% S.F. 96 on Chromasorb WHP, 68/80-mesh, 0.32 cm by 4.6 m. A nitrogen carrier stream flowing at 45 ml/min was delivered through the column to a flame ionization detector at 200°C, supplied by hydrogen at 40 ml/min and by air at 280 ml/min. One column was maintained at 30°C and was used to separate the isoflurane, halothane, and enflurane. Retention times were 3, 3.5, and 5 min, respectively. The second column was kept at 80°C and was used to separate methoxyflurane from the other vapors. Results were recorded separately on a dual-channel strip recorder. To ensure the accuracy of these measurements, we measured calibration standards (prepared as described previously (7)) at intervals during each study. Peak heights were proportional to concentration over the entire range of concentrations studied.

The ratio of F_A to F_I (F_A/F_I) was used to define the washin of anesthetic. The ratio of F_A to F_{AO} (F_A/F_{AO}) was used to define the washout of anesthetic. F_{AO} is the alveolar concentration of anesthetic immediately before discontinuation of anesthetic administration.

Multiexponential (multicompartment) models of the form

$$\sum_{i=1}^{n} \frac{A_i}{\lambda i}(1 - e^{-\lambda_i t}) \qquad (1)$$

and

$$\sum_{i=1}^{n} A_i e^{-\lambda_i t} \qquad (2)$$

were fit to the washin and washout data, respectively, using least-squares analysis (10). We fit equations (models) having successively more exponents (interpreted as compartments) to the data for each anesthetic for each patient (i.e., for each of the 36 data sets that we obtained). For each data set, the model having the greatest number of compartments (highest n) that significantly decreased the residual sum of squares when compared with the model having one less compartment ($n - 1$) was considered to provide the "best fit" ($P < 0.05$, F–ratio test (11)).

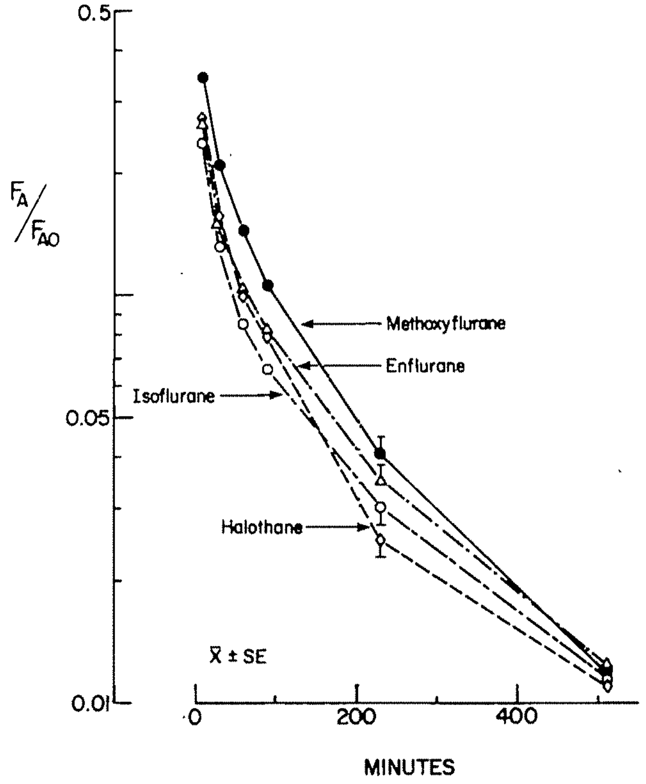

Figure 2. The decline in the alveolar concentration is expressed as the ratio of the alveolar partial pressure at a given time (F_A) to the alveolar concentration immediately before discontinuation of anesthetic administration (F_{AO}) and is plotted against time (means for all data ± SE for 2- and 4-day values). Note that F_A/F_{AO} is plotted on a longarithmic scale.

Time constants were calculated as $1/\lambda_i$ for each compartment. The time constants, for each compartment of the five-compartment models, were compared among the anesthetics. The statistical significance of any difference was assessed using paired t-tests with the Bonferroni correction for multiple comparisons (12).

Results

The curve for washin (F_A/F_I) increased most rapidly with nitrous oxide and least rapidly with methoxyflurane (Fig. 1). for the other agents, the rate of increase was in accord with their respective solubilities in blood. These relationships were not maintained during washout (Fig. 2). The washout (F_A/F_{AO}) curve

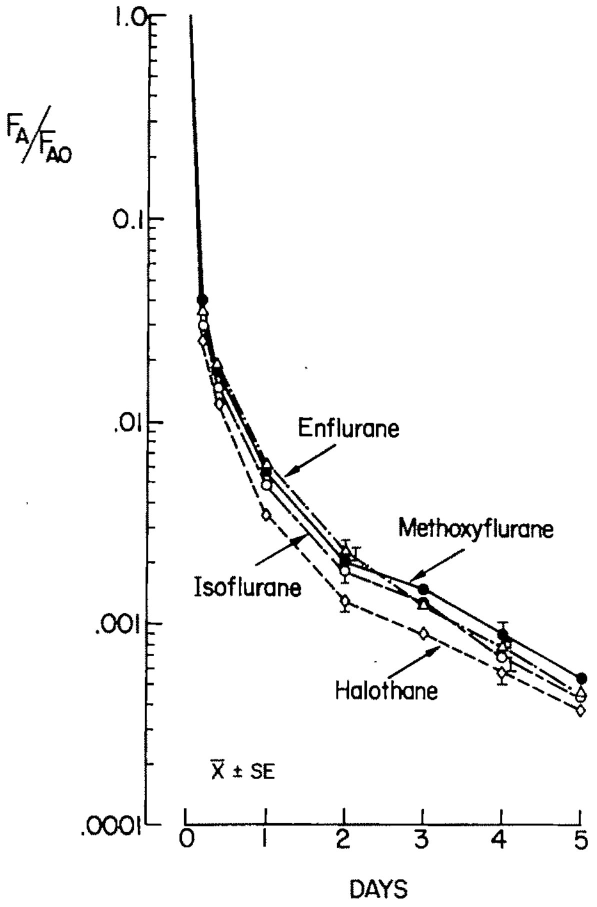

Figure 3. The interval from 10 to 500 min during alveolar washout is shown to illustrate the position of the anesthetic washout curves. The ratio of the alveolar concentration at a given time (F_A) to the alveolar concentration immediately before discontinuation of anesthetic administration (F_{AO}) is plotted against time (means for all data ± SE for the 230-min data). Note that F_A/F_{AO} is plotted on a logarithmic scale.

for halothane fell below that for enflurane after 69 ± 16 min of washout and below that for isoflurane after 203 ± 25 min. Similarly, the ratio for methoxyflurane fell below that for enflurane after 760 ± 166 min (Fig. 3). The terminal portions of the washout curves were remarkably close for all anesthetics and were rectilinear for as long as they were measured (Fig. 3).

The alveolar washin data were best fit by a two-compartment model for 26 of the 36 data sets (four anesthetics in each of nine patients) and by a three-compartment model for the other ten data sets (Table 1). No four-compartment model provided a better fit. Although some data sets were best fit by three-compartment models, the mean coefficients of variation for the third compartment time constants were as high as 2.68.

Analysis of the alveolar washout allowed definition of more compartments than analysis of the washin. Slowly equilibrating compartments were only identified during washout. The washout was best fit by a four-compartment model for 9 of the 36 data sets and by a five-compartment model for 27 of the 36 data sets (Tables 2 and 3). A six-compartment model did not provide a significantly better fit for any data set. The maximum mean coefficients of variation of the time constants determined for compartments one through five were 49, 40, 19, 22, and 11%, respectively. For any one compartment, the time constants were similar for all four anesthetics.

Discussion

The F_A/F_I ratios for the five anesthetics were similar to those reported previously by others, and qualitatively related to each other as predicted by the respective blood/gas partition coefficients of the different anesthetics (Fig. 1). The differences between the isoflurane and enflurane ratios were similar to the differences between the ratios for enflurane and halothane, a relationship that is consistent with their differences in partition coefficients. Examination of F_A/F_I ratios for these anesthetics from studies done by separate investigators in different subjects do not show quite the same relationship. Cromwell et al. (13) found F_A/F_I ratios for isoflurane that were close to the ratios found by Munson et al. (6) for enflurane. However, Munson et al. found a separation for enflurane and halothane that was three times as great as the modest separation between enflurane and isoflurane. The inconsistency of these findings with the results predicted by the partition coefficients illustrates the difficulty of comparing the pharmacokinetic properties of anesthetics between studies.

In contrast to the F_A/F_I ratios, our F_A/F_{AO} ratios were not entirely consistent with what might have been predicted from the blood/gas partition coefficients. The halothane ratios decreased more rapidly than those for isoflurane and enflurane, despite the greater solubility of halothane. Similarly, the F_A/F_{AO} ratios for methoxyflurane fell below those for enflurane, even though methoxyflurane is approximately six times more soluble than enflurane. This phenomenon has been previously reported for halothane at subanesthetic concentrations (6,7), but not for methoxyflurane. The more rapid decrease of the values for both halothane and methoxyflurane in large part can be attributed to the elimination of these agents via the liver (7). Both agents undergo considerable biodegradation, whereas enflurane and isoflurane undergo relatively minimal biodegradation (1,2,14–16). If this interpretation is correct, it suggests that metabolism of anesthetic can significantly affect the rate

Table 1. Time Constants ($1/\lambda_i$) Determined by Multicompartmental Analysis of Alveolar Washin (min)

Compartment	Isoflurane	Enflurane	Halothane	Methoxyflurane
For curves "best fit" by a two-compartment model				
	(n = 5)	(n = 6)	(n = 6)	(n = 9)
1	0.20 ± 0.01	0.26 ± 0.03	0.20 ± 0.03	0.14 ± 0.02
2	6.50 ± 1.93	7.52 ± 1.99	6.07 ± 2.07	6.44 ± 3.59
For curves "best fit" by a three-compartment model				
	(n = 4)	(n = 3)	(n = 3)	(n = 0)
1	0.19 ± 0.05	0.15 ± 0.03	0.12 ± 0.04	—
2	3.17 ± 0.54	2.71 ± 0.45	2.59 ± 0.54	—
3	71.63 ± 21.06	90.91 ± 22.33	121.83 ± 47.47	—

Data are expressed as mean ± SE.

of recovery from halothane and methoxyflurane anesthesia.

The specific concentration of anesthetic at the start of anesthetic administration may determine the influence of metabolism on the rate at which the washout curve falls. In contrast to the results of Cahalan et al. (7), Torri et al. (5) did not observe accelerated elimination of halothane after simultaneous administration of halothane and enflurane to patients undergoing minor surgery. Cahalan et al. observed that the washout curve for halothane crossed that for enflurane at an end-tidal concentration of halothane of 0.0075–0.033%. Torri et al. administered anesthetizing concentrations and followed washout for only 60 min, at which time we estimate that the average end-tidal concentration of halothane was 0.055%, i.e., above the range in which Cahalan et al. observed the curves to cross. An accelerated elimination of halothane may not have been observed by Torri et al. because the partial pressure of halothane in the liver had not decreased below the Km (the partial pressure of anesthetic at which the rate of metabolism is half the maximum rate of metabolism) for metabolism of halothane. This explanation is supported by the results of Sawyer et al. (9), which suggest that the Km for halothane may be 0.01 MAC, or less than 0.01% halothane.

Comparison of the washin and washout data demonstrates the difficulty of defining the pharmacokinetic properties of inhaled anesthetics by examining washin data. Such data cannot be collected over a long enough period of time to permit a demarcation of the compartments that equilibrate more slowly. For most of our data sets, even the 2-hr period of washin did not permit the definition of more than two compartments. In contrast, in 75% of our data sets washout data revealed five compartments.

The time constants obtained for our compartments 2, 3, and 5 correlated with those predicted from known tissue blood flows and solubilities for the vessel-rich, muscle, and fat tissue groups, respectively (Table 3). That is, these data are consistent with present interpretations of the impact of the major tissue groups governing the pharmacokinetics of inhaled anesthetics. Also consistent is the finding that the rate constants for a given compartment were similar among the different anesthetics. This follows because the factors governing the rate constant would be predicted to be the same. Because the anesthetics were administered concurrently, blood flow must be the same; tissue volume must be the same for the same reason; and the measured tissue/blood partition coefficients are close to each other despite the dissimilarity of the blood/gas partition coefficients. The small but significant differences found among the anesthetics for the fifth compartment (Table 3) would be predicted from the measured differences in the fat/blood partition coefficients for these agents.

The minor differences that exist between our data and predicted values probably result in part because the time constants provided by our analysis are hybrid rate constants. They are influenced by more than the compartment in question. That is, the rate of change at any particular time in the washout process is not purely the result of one compartment but rather the net effect of the rates of change occurring in all compartments at that time. However, each hybrid rate constant differs from adjacent rate constants by at least a factor of 6. This separation diminishes the influence of adjacent rate constants on each other. Since the terminal rate constant has no subsequent constant, it should be least influenced and most accurate. The correlation of our results with predicted rate constants should be closest for this constant. It is. Because the first-compartment rate constant has four subsequent constants, it may be most influenced and therefore least accurate. This potential for error may partly explain the differences between the hybrid rate constants we determined for the first compartment and

Table 2. Coefficients (A_i) for Five-Compartment Models of Alveolar Washout

Compartment	Isoflurane ($n = 7$)	Enflurane ($n = 7$)	Halothane ($n = 7$)	Methoxyflurane ($n = 6$)
1	5629 ± 283	5156 ± 326	5401 ± 218	5030 ± 430
2	2604 ± 149	2712 ± 172	2517 ± 147	2029 ± 193
3	1341 ± 166	1635 ± 185	1704 ± 173	2497 ± 269
4	265 ± 50	327 ± 70	214 ± 41	338 ± 100
5	38 ± 5	56 ± 7	28 ± 4	51 ± 7

Data are expressed as mean ± SE.
All values are multiplied by 10^4.

Table 3. Calculated Time Constants ($1/\lambda_i$) for Five-Compartment Models of Alveolar Washout Compared with Those Predicted Using Current Interpretations of Uptake and Distribution

	Isoflurane ($n = 7$)	Enflurane ($n = 7$)	Halothane ($n = 7$)	Methoxyflurane ($n = 6$)
Calculated time constants (min)				
Compartment				
1	0.19 ± 0.03[a]	0.16 ± 0.03[a]	0.16 ± 0.03	0.11 ± 0.01[b]
2	6.72 ± 1.26	6.67 ± 1.16	7.46 ± 1.24	7.76 ± 1.04
3	77.0 ± 8.4	73.4 ± 6.6	75.6 ± 7.3	73.5 ± 5.2
4	500 ± 163	503 ± 65	480 ± 59	529 ± 64
5	3465 ± 176[a]	2963 ± 130[a]	3842 ± 199[a]	3231 ± 469
Predicted time constants (min)				
Pulmonary washout	0.50	0.50	0.50	0.50
VRG	2.69	2.10	3.00	1.48
MG	50.7	36.3	47.7	33.0
FG	2545	2005	3135	2820

Data are expressed as mean ± SE.
Abbreviations: VRG, vessel-rich group; MG, muscle group; FG, fat group.
[a] Significantly different from each other for this compartment ($P < 0.008$).
[b] Significantly different from the other three anesthetics for this compartment ($P < 0.008$).

those predicted for washout of the lung. In addition, the volume we assumed for the functional residual capacity (FRC) of the lung (2 L) is probably greater than the actual FRC of our patients, who were positioned with the kidney rest elevated. This smaller FRC would result in a faster rate of equilibration, and thus a shorter time constant, for the first compartment.

We found one more tissue compartment (the fourth compartment; Table 3) than did previous studies (1,2,15). Holaday et al. (2) might have found this compartment had they not confined their analysis to three "tissue" compartments. This constraint may also explain the difference between the rate constants they determined for the muscle and fat groups and those predicted from blood flow, tissue volume, and tissue solubility. The failure to parcel out the effect of the fourth compartment would tend to increase the time constant for the muscle group and to decrease the time constant for the fat group (i.e., would tend to draw these values together).

The composition of the fourth compartment is not easily explained. The only tissue group that we would predict to have a time constant in the range of that found for the fourth compartment is red marrow. A 70-kg human has about 1400 ml of red marrow that is composed of approximately 40% fat and 60% lean tissues and has a blood flow of approximately 10 ml·100 $\text{ml}^{-1}\cdot\text{min}^{-1}$ (16,17). Tissue/gas partition coefficients for inhaled anesthetics in red marrow have not been measured but can be roughly estimated by combining known fat and lean tissue coefficients. Isoflurane's marrow/gas partition coefficient should be approximately 42.3 (i.e., 0.40·fat/gas partition coefficient + 0.60·lean tissue/gas partition coefficient (18)). The time constant calculated from these values would be about 250 min. A decrease in blood flow or an increase in solubility could increase the time constant for red marrow into the range of our fourth compartment. A compartment with a time constant of 500 min would become approximately 21.3% equilibrated with the delivered partial pressure during a 2-hr administration (i.e., $1 - e^{-(120/500)}$). If the delivered partial pressure of anesthetic is estimated as the end-tidal partial pressure achieved at the end of the anesthetic administration (0.002676, for isoflurane), we can estimate the volume of anesthetic gas that would actually distribute to red marrow to be 33.8 ml for isoflurane (1400 ml·42.3·0.213·0.002676). In contrast, an average of 119.3 ml of isoflurane was recovered from the fourth compartment; 33.7% of the total (354 ml) isoflurane recovery (unpublished data). If red marrow contributes to the fourth compartment it accounts for only about 28% of the anesthetic recovered from the fourth compartment.

The time constant for our fourth compartment cannot be explained by blood flow or solubility characteristics of any other known tissue group. If this compartment is composed of muscle, either tissue solubility would have to increase sevenfold or blood flow would have to decrease sevenfold. If this compartment were composed of fat, the converse would have to be true. No studies of blood flow or solubility support these explanations.

We speculate that our fourth compartment is composed of fat immediately adjacent to highly perfused tissue and has access to anesthetic by intertissue diffusion. Examples of such fat groups would include omental fat, perirenal fat, pericardial fat, and subcutaneous fat. This hypothesis has been suggested previously (19,20), and the concentration gradients of inhaled anesthetics in perirenal fat have been documented (21). However, we stress that this is simply a plausible hypothesis and that no direct evidence for it is present in our data.

One may wonder whether one anesthetic would influence the pharmacokinetic properties of another anesthetic administered simultaneously. For example, anesthetics administered simultaneously could compete for solvent sites and thereby alter individual anesthetic solubility. However, previous studies have found comparable anesthetic solubilities regardless of whether the determinations were made for individual anesthetics or for mixtures of anesthetics (18,22–24). Also, simultaneous administration of anesthetics may result in inhibition of the metabolism of one agent by another (25,26). However, we have also measured metabolism during simultaneous administration of anesthetics (to be reported separately), and our results quantitatively agree with or exceed those from previous studies of metabolism in which only single anesthetics were administered. In addition, the rapid decay rates of halothane and methoxyflurane are readily explained only by an appreciable rate of metabolism of these anesthetics.

Our approach to the measurement of the pharmacokinetic properties of inhaled anesthetic has at least one deficiency. Simultaneous administration eliminates the ability to detect the effect of pharmacologic differences that may affect the pharmacokinetic characteristics of anesthetics. For example, alterations in cardiac output or distribution of blood flow that may be caused by only one anesthetic will affect the pharmacokinetic characteristics of all four anesthetics. However, we believe the advantages of simultaneous administration, specifically the absence of interindividual variability when comparing the pharmacokinetic properties of these agents, greatly outweigh this disadvantage.

Finally, the identification of distinct anatomical tissues on the basis of separable "exponentials" on a washout curve, and the further assignment of such tissues to specific anatomical sites on the basis of observed time constants and known tissue volumes, partition coefficients, and blood flows is fraught with uncertainty. It is well-known, for example, that tissues with time constants separated by a factor of only 2 may "merge," creating an intermediate time constant that will not reflect the time constant of either compartment accurately. Thus although our model is consistent with a direct physiologic interpretation, this consistency cannot be seen as sufficient evidence to prove this interpretation. However, regardless of how these compartments are interpreted, the identification of five distinctly separated compartments suggests that the previous model is inadequate: a five-compartment model defines more accurately the pharmacokinetic properties of inhaled anesthetics than does a four-compartment model.

In summary, slowly equilibrating compartments could be identified only by examining the alveolar washout for a prolonged period. Although our results are generally in accord with those for the four-compartment model of uptake and distribution, we consistently found a new compartment equilibrating at a rate that lies between the rates predicted for the muscle and fat tissue groups. We suggest that the four-compartment model may need modification to include this new compartment. Finally, we document an accelerated rate of halothane and methoxyflurane elimination that we attribute to metabolism of these anesthetics.

Isoflurane (Forane®) and enflurane (Ethrane®) were donated by Anaquest. Halothane (Fluothane®) was donated by Ayerst Laboratories.

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Distribution in Cerebrospinal Fluid, Blood, and Lymph of Epidurally Injected Morphine and Inulin in Dogs

Philippe A. C. Durant, MD, and Tony L. Yaksh, PhD

DURANT PAC, YAKSH TL. Distribution in cerebrospinal fluid, blood, and lymph of epidurally injected morphine and inulin in dogs. Anesth Analg 1986;65:583–92.

We describe procedures for catheterizing the epidural space, the azygos vein, and the thoracic lymph duct of dogs without using fluoroscopy. The success rates of the procedures were 100, 80, and 50%, respectively ($n = 10$). To assess the validity of the model, ^{3}H-morphine and unlabeled morphine (2 mg) were injected epidurally in ten dogs. Lumbar cerebrospinal fluid (CSF), azygos venous blood, arterial blood, and lymph were sampled before and 5, 20, 60, 120, 180, 240, 300 and 360 min after injection. During the first 20 min, morphine levels in the azygos vein were about three and ten times greater than arterial and lymphatic levels, respectively ($n = 3$; $P < 0.01$). Morphine levels were significantly greater in the azygos vein ($n = 8$) and the femoral artery ($n = 10$) during the first 20 and 60 min than they were later, respectively ($P < 0.05$). In the lymph ($n = 5$), the levels of morphine at 60 min were statistically greater ($P < 0.05$) than levels at 4, 5, and 6 hr. At no time were the concurrent arterial and lymph levels different from each other. In the lumbar CSF, the morphine peak concentration was reached 5–60 min after epidural injection and ranged between 5 and 93 μg/ml. In the CSF, the levels of morphine were significantly greater during the first 20 min than later ($n = 7$; $P < 0.05$). The washout of the lumbar CSF curve for morphine appeared to be fitted by a two-compartment open model. The $t_{1/2}$-α and $t_{1/2}$-β values were 14.7 ± 7.2 min and 106 ± 45 min, respectively (mean ± SD). Cumulative percentages of the epidural dose of morphine passed into the azygos system within the first 5, 20, 60, and 120 min after injection were calculated to be 4.0 ± 2.1, 23.5 ± 14.6, 49.2 ± 34.2, and 55.9 ± 35.3, respectively (mean ± SD; $n = 8$). Both ^{14}C-inulin and ^{3}H-morphine were injected epidurally in one dog and intrathecally in another dog. In the CSF, morphine appears to be cleared at a rate similar to that of inulin. The fraction of morphine and inulin crossing the dura after epidural injection was calculated to be 0.31% and 0.59%, respectively.

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—morphine. ANALGESICS—morphine.

Epidurally administered drugs may enter the cerebrospinal fluid (CSF), the epidural venous blood, and lymph and become partitioned in the epidural fat. The epidural veins drain into the azygos vein. The lymphatic vessels surrounding the dural root sleeves drain into longitudinal channels in front of the vertebral column. Calculations of the kinetics of drugs administered by the epidural route require an animal model that assesses the concentration of drug in the CSF, the azygos vein, the systemic circulation, and the lymph.

Because the lumbar vertebrae overlap, the epidural space of the dog is routinely catheterized by laminectomy (1,2), by laminotomy (3), or by burring a hole in the sacrum (4). These techniques are time-consuming, and, with the first two approaches, the risk of perforating the dura is significant. The azygos vein of the dog can be catheterized by cannulation of the superior intercostal vein through a right thoracotomy incision (4) or by cannulation of the external jugular vein, the tip of the catheter being introduced in the ostium of the azygos vein under fluoroscopy (K. Samii, M. Stanton-Hicks, H. Wüst, C. Rowley: unpublished observations).

The present paper describes reliable techniques for catheterizing without fluoroscopy the epidural space, the azygos vein, and the thoracic lymph duct in dogs. To assess the validity of the model, ^{3}H-morphine was injected epidurally in ten dogs. To compare the disposition of morphine with a marker of extracellular water and to assess the amount of drug crossing the dura, one dog (number 7) received both ^{14}C-inulin and ^{3}H-morphine epidurally, and an eleventh dog received the two labeled agents intrathecally.

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Address correspondence to Dr. Yaksh, Department of Neurosurgical Research, Mayo Clinic, Rochester, MN 55905.

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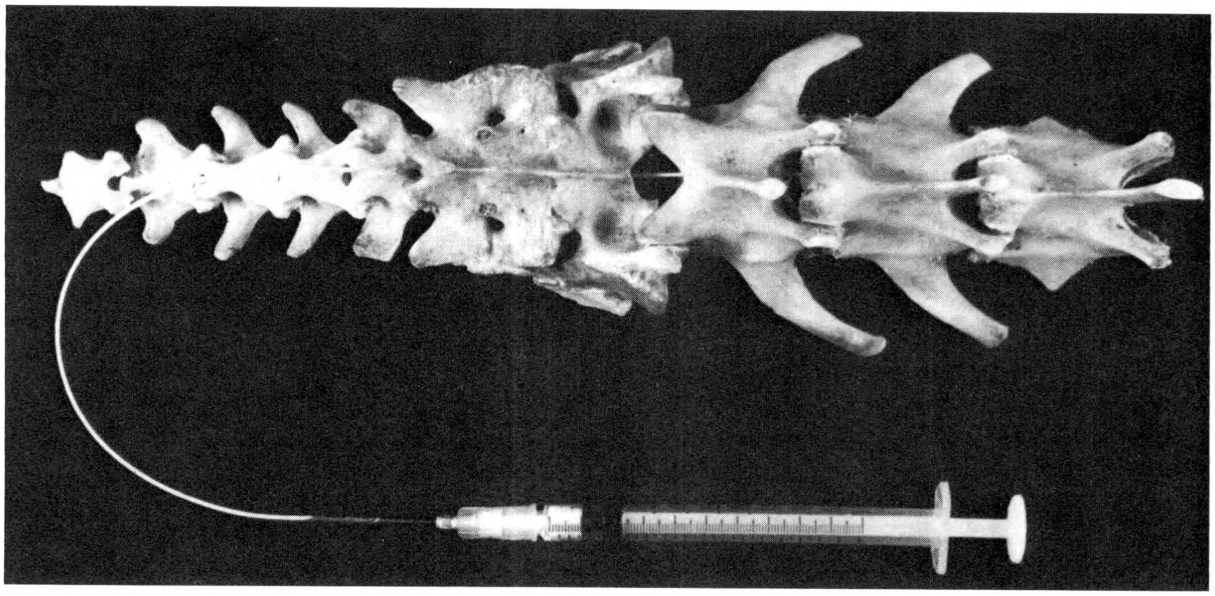

Figure 1. Posterior view of lower vertebral column (L5–Co5) of the dog. PE50 epidural catheter is inserted between coccygeal vertebrae 1 and 2, and can be seen in the vertebral canal between L7–S1. Tuberculin syringe (1 ml) provides an approximate scale.

Methods

Preparation of Catheters

To make the catheters, polyethylene tubing (PE50, 0.6 mm inside diameter (ID) and 1.0 mm outside diameter (OD)) were cut into segments of 60 cm (intrathecal catheter), 40 cm (epidural catheter), and 15 cm (azygos catheter).

Animal Preparation and Surgical Procedure

Eleven mongrel dogs of either sex were used in this study (mean weight ± SD: 14.4 ± 1.6 kg). The National Research Council's guide for the care and use of laboratory animals was followed.

Anesthesia. The dogs were anesthetized with sodium pentobarbital (20–30 mg/kg) and paralyzed with succinylcholine 1–2 mg/kg, both administered intravenously. The trachea was intubated and a femoral arterial catheter inserted. Animals were ventilated with intermittent positive pressure ventilation (IPPV) using a Harvard model 901 respirator. Tidal volume was normally between 200 and 250 ml. Respiratory rate was 20 breaths/min and adjusted according to arterial blood gas values. Pancuronium, 0.1 mg/kg intravenous, was administered periodically.

Thoracic duct cannulation. The dog was positioned in the right lateral decubitus position. The left forepaw was then retracted caudally in order to move the left scapula backwards. On the left side of the neck, an incision about 15 cm long was made parallel to the external jugular vein. The junction of this vein with the subclavian vein was carefully dissected. Once the thoracic duct was identified, cannulation with a polyethylene tubing (PE100, 0.9 mm ID and 1.5 mm OD) was achieved. The dissection was delicate, and the median time required was 45 min (range 30–90 min). Then, the dog was placed in the sphinx position and the head placed forward in a stereotaxic holder. The cisterna magna was maintained approximately 6 cm above the level of the lumbar spinal cord.

Epidural space catheterization. The sacro-coccygeal area was shaved, and a transverse skin incision about 2 cm long was made between the third sacral (S-3) and first coccygeal (Co-1) vertebrae, between Co-1 and Co-2 (Fig. 1), or Co-2 and Co-3. At the base of the spinous process, the yellow ligament was pierced with the tip of a scalpel blade. The distance between the thoracolumbar junction and the incision was then measured and a black mark made on the catheter at that distance. The catheter was then gently twisted and introduced cephalad into the lumbar epidural space up to the black mark (Fig. 2). The procedure required approximately 3 min. As shown in Figure 1, the catheter can be inserted between Co3–4, Co4–5 or L7–S1 as well. However, at the lumbosacral junction, the depth at which the epidural space is encountered increases considerably. Such anatomy makes catheterization more difficult. It is worth noting that, in dogs, the caudal end of the spinal cord and the dural sac is located at L-6 and L-7 levels, respectively. The coc-

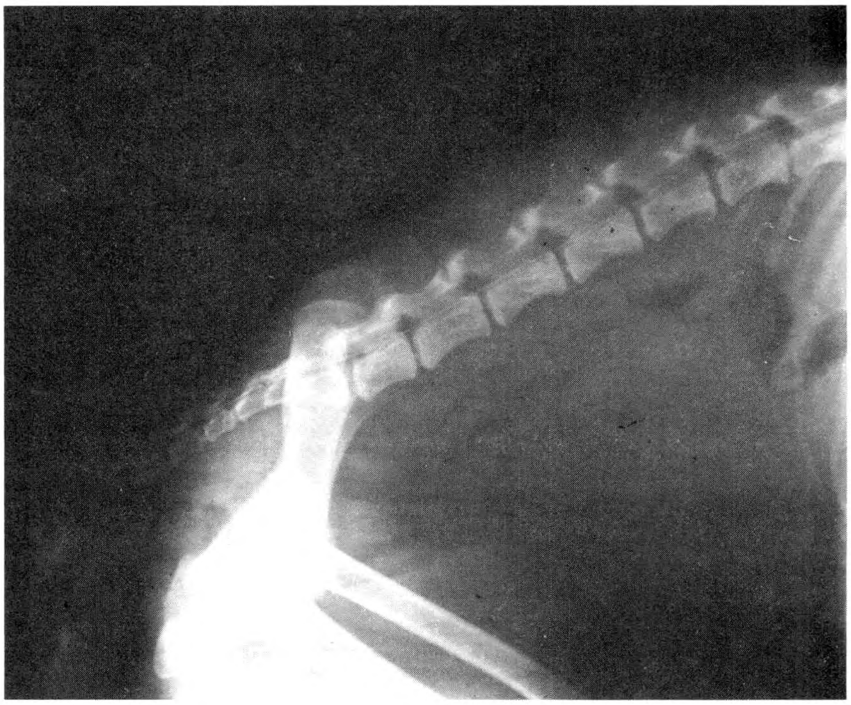

Figure 2. Epidural space catheterization. The PE50 catheter was introduced between the first and the second coccygeal vertebrae and inserted cephalad up to the thoracolumbar junction (25 cm). The tip of the catheter is located on the edge of the picture. Hypaque 50% 0.1 ml was injected in the epidural catheter.

cygeal approach was found also to be applicable in cats (unpublished observations).

Azygos vein catheterization. A midline longitudinal skin incision was made between the fifth and the tenth (T5–10) thoracic spinous processes. The skin on the right side of the chest was lifted up. At the upper, lower, and midpoint of the chest, three subcutaneous veins are usually present and can be seen easily on the internal surface of the skin. These veins drain into intercostal veins. According to Evans et al. (5), these veins might be the satellite veins of the distal lateral cutaneous branches of the intercostal arteries. In our experience, the upper vein is not readily cannulated because its path is tortuous. The two lower veins can be readily cannulated most of the time and drain into the seventh and the eleventh intercostal veins, respectively. The intercostal veins travel to intersect the azygos vein at a right angle. After careful dissection of the subcutaneous fat and after proximal ligation of one subcutaneous vein, a small cut was made in the subcutaneous vein close to its junction with the intercostal vein. The catheter was then introduced into the vein. After about 6 cm, significant resistance was felt, indicating that the tip of the catheter was then lying just within the azygos vein. Such an end point is adequate, and samples can be withdrawn from such catheters. Occasionally, twisting the catheter for 10–15 min or injecting saline allowed a further insertion of the catheter, the distal end being then located closer to the superior vena cava (Fig. 3). Further attempts were usually unsuccessful. Median dissection time was 47 min (range: 20–70 min). To avoid trauma to the pleura, dissection of the intercostal muscle should be avoided.

Intrathecal space catheterization. The dura between the foramen magnum and the first cervical vertebra (C-1) was exposed by a midline dissection of the posterior muscles of the neck through a skin incision, which extended from the occipital protuberance caudally for 6 cm. A 1-mm incision was made in the cisternal membrane on midline, approximately 2 mm caudal to the dorsal edge of the foramen. A blunt hook was inserted to assure retraction of the dura and the underlying arachnoid. Approximately 40 cm of PE50 tubing was passed down to the level of the thoracolumbar junction.

Injectate and Sampling

In dogs, the vertebral formula is C-7, T-13, L-7, S-3, Co-20. Over a weight range of 11.0–15.7 kg, the spine length is fairly constant. From the Co1–2 junction up to L5–6 ($n = 10$), L2–3 ($n = 12$), and T13–L1 ($n = 9$) junctions, the spine length was 13.1 ± 2.2 cm, 16.5 ± 1.9 cm, and 24.6 ± 3.3 cm, respectively (mean ± SD, unpublished observation). In addition, epidural injection of radioopaque dye 2 ml (hypaque 50%) in the upper lumbar region in four dogs spread

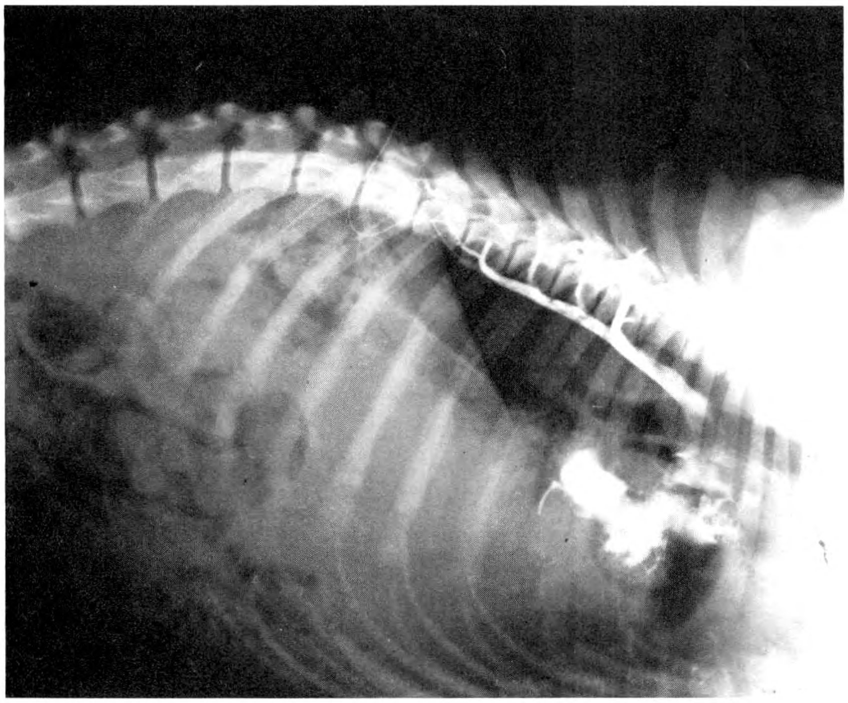

Figure 3. Azygos vein catheterization. The PE50 catheter was introduced in the cutaneous branch of the T11 intercostal vein (12 cm). The tip of the catheter was located 6 cm from the superior vena cava. Hypaque 50%, 5 ml, was injected in the azygos catheter. Four venous connections between the epidural venous plexus and the azygos vein are opacified. Some dye is present in the superior vena cava and the right cavities of the heart.

over ten to 14 segments (segment range: T7–L7; weight range: 13–15.7 kg). Therefore, the volume of the epidural injectate was not adjusted for dog size.

Morphine (2 mg) containing ^{3}H-labeled morphine 1 μCi/ml specific activity was diluted in 2 ml of 0.9% saline and injected via the epidural catheter in ten dogs. The lumen of the catheter was then flushed with 0.1 ml saline. In addition to ^{3}H-morphine, dog number 7 received ^{14}C-labeled inulin carboxylic acid (Amersham) 1 μCi/ml specific activity epidurally. An eleventh dog received the two labeled compounds intrathecally in 0.6 ml of 0.9% saline.

Samples of CSF (0.2 ml), azygos venous blood (1 ml), arterial blood (1 ml), and lymph (1 ml) were collected simultaneously before and 5, 20, 60, 120, 180, 240, 300, and 360 min after injection. After each sample, CSF was replaced by an equivalent volume of artificial CSF. The heparinized blood samples were spun and the plasma collected. Fifty μl aliquots of each sample were added to scintillation phosphor. Radioactivity was measured in a Beckman scintillation counter and converted to counts per minute.

Necropsy

All animals were killed by an overdose of pentobarbital at the end of the experiment. X-rays after injection of Hypaque 50% in all catheters were performed and followed by laminectomy and right thoracotomy to confirm the appropriate position of the catheters.

Statistics and CSF Decay Curve Analysis

All data points were normalized to 10^6 counts/min of injectate. Radioactivity values were converted to ng/ml. One-way analysis of variance with repeated measures on the same elements was employed to compare morphine levels within each compartment (CSF, lymph, azygos blood, or femoral blood). The same analysis was used to compare morphine levels between compartments at each specific collection time. The differences between morphine levels were analyzed by the Newman–Keuls method (6).

Pharmacokinetic calculations of lumbar CSF decay curves were performed using the NONLIN least squares regression analysis computer program (7). Areas under the time-concentration curves (AUC) were measured by the trapezoidal rule and expressed in (min × ng/ml) × 10^3 (8).

Absorption by Epidural Veins

For each dog, the fraction of the morphine epidural dose (ng) removed by the epidural veins as a function of time was calculated by multiplying the azygos vein flow (ml/min) by the difference between the AUC in the azygos vein and the AUC in the femoral artery (min × ng/ml) such that fraction removed = flow × $(\text{AUC}_{\text{Az}} - \text{AUC}_{\text{Art}})$. Fraction values were converted in percent of the total dose. The flow in the azygos vein was taken to be 101 ml/min, based on the mean

Table 1. Epidural Injection of Morphine (2 mg): CSF Decay Curves

Dog	Weight (kg)	t½-α (min)	t½-β (min)	AUC (min × ng/ml) × 10^3	Morphine peak in CSF: Concentration (ng/ml) × 10^3	Morphine peak in CSF: Time after injection (min)
1	15.0	23.0	176	4884	92.9	5
2	11.5	20.5	125	839	10.3	20
3	13.75	—	—	671	5.4	20
4	15.6	13.0	86	1692	47.7	5
5	15.7	—	—	584	5.2	60
6	14.6	12.0	80	3005	58.0	20
7	12.8	5.0	63	684	27.4	5
mean ± SD		14.7 ± 7.2	106 ± 45.2	1766 ± 1627		

Abbreviations: t½-α, initial elimination half-life; t½-β, terminal elimination half-life; AUC, area under the concentration–time curve up to 6 hr; —, data not available for lack of sufficient points to define the second phase.

Data of dog numbers 2, 6, 7 are shown in Figures 4 and 5. Azygos data of dogs 2–7 are shown in Table 2.

resting value observed by Burfoot and Bromage in the anesthetized dog (4).

Results

Catheterization Procedures

The thoracic duct could be cannulated in five of ten dogs. Failure to catheterize the duct was due to anatomical factors. About one-half of the time, the thoracic duct terminates singly and presents a terminal dilation immediately before perforation of the venous wall. In this case, cannulation is easy. In other specimens, however, the cranial portion of the thoracic duct bifurcates or trifurcates. These branches are usually connected by cross branches so that a coarse, widespread plexus is formed (5). Such anatomy makes cannulation difficult.

The epidural catheter was located at the expected level in all animals ($n = 10$). In addition, the technique was performed in 21 other dogs (unpublished observations). In the latter group, one of 21 catheters curled up after 15 cm of insertion. In that instance, some resistance was felt and the insertion was pursued. If this happens, the catheter sould be withdrawn gently and then reinserted. No epidural hematomas were noticed at necropsy.

The azygos vein was successfully catheterized in eight of ten animals. Almost no resistance was felt during insertion of two catheters whose distal end was located 15 cm from the site of cannulation and about 5 cm from the superior vena cava (SVC). The technique was performed in 21 additional dogs. Cannulation was successful in 16 dogs, among which the tip of six catheters were located close to the SVC (unpublished observations). The success rate was similar with the middle and the lower cutaneous vein approaches.

In seven of ten animals in which catheters were also inserted into the subarachnoid space, the tip of the intrathecal catheter was located immediately adjacent to the epidural catheter tip.

Morphine Distribution

Simultaneous collection of samples in the four compartments (CSF, lymph, azygos blood, arterial blood) was possible in three dogs (number 2, 6, 7 in Tables 1 and 2). Mean log concentration-time curves based on levels assessed concurrently in each compartment are shown in Figures 4 and 5 for three animals. Comparison of morphine levels within each compartment shows that azygos levels at 5 and 20 min were not statistically different from each other but were significantly greater ($P < 0.01$) than levels at 60 min and later ($n = 8$). In two of eight dogs, azygos levels were very low (Table 2). Lumbar CSF levels of morphine were observed to vary from one dog to another (Table 1). Statistical analysis of CSF levels in seven dogs after epidural morphine shows, however, that during the first 20 min, morphine levels are significantly greater than levels at 60 min ($P < 0.05$) and later ($P < 0.01$). The CSF levels at 5 and 20 min were not statistically different from each other. In the femoral artery, morphine levels at 5, 20, and 60 min were not statistically different from each other but were significantly greater ($P < 0.05$) than levels at 3 hr and later ($n = 10$). In the thoracic duct, the levels of morphine at 60 min were significantly greater ($P < 0.05$) than levels at 4, 5, and 6 hr ($n = 5$).

Comparison of morphine levels between compartments showed that morphine levels in the azygos vein were significantly greater than the arterial and lymph levels during the first 20 min after injection ($P < 0.01$) but not at 60 min and later ($n = 3$). At no time were

Table 2. Cumulative Percentage of Epidurally Injected Morphine (2 mg) Recovered from Azygos Vein

	Time after epidural injection (min)			
Dog	5	20	60	120
1	—	—	—	—
2	3.8	35.0	88.6	90.9
3	1.5	5.6	5.6	5.6
4	0.7	2.2	8.9	8.9
5	4.4	24.3	48.1	54.6
6	4.5	23.1	47.2	70.1
7	7.1	45.1	100.0	100.0
8	6.0	33.6	63.5	75.4
9	3.9	19.1	31.5	41.4
mean ± SD	4.0 ± 2.1	23.5 ± 14.6	49.2 ± 34.2	55.9 ± 35.3

Dog numbers 1–7 are the same as Table 1.
Data from dogs 2, 6, 7 are shown in Figures 4 and 5.
— not available.

the concurrent arterial and lymph levels different from each other. In addition, Figure 4 shows with concurrently measured levels that during the first 3 hr, the rate of elimination of morphine from CSF and azygos blood is the same.

CSF Decay Curves and Estimation of Diffusion Across the Dura

Lumbar CSF decay curves were fit to a two-compartment open model (with 1/y weighting factor). Table 1 shows that the mean (± SD) of the initial ($t_{1/2}$-α) and terminal ($t_{1/2}$-β) elimination half lives were 14.7 ± 7.2 min and 106 ± 45.2 min, respectively. The morphine peak concentration in the CSF was reached 5 to 60 min after epidural injection and varied from 5.2 to 93 μg/ml. The mean (± SD) AUC value for morphine in the CSF up to 6 hr was 1766 ± 1627 (ng/ml × min × 10^3; $n = 7$).

After epidural (dog number 7) or intrathecal (dog number 11) injection of both inulin and morphine, the morphine/inulin AUC ratios in CSF were 0.39 and 0.73, respectively. The epidural/intrathecal AUC ratios in CSF, as an estimation of the amount of drug diffusing across the dura, were 0.0031 for morphine and 0.0059 for inulin.

Drug Removal by the Epidural Veins

Table 2 shows cumulative percentages of the epidural dose of morphine passed into the azygos system within the first 5, 20, 60, and 120 min after injection: 4.0 ± 2.1, 23.5 ± 14.6, 49.2 ± 34.2, and 55.9 ± 35.3, respectively (mean ± SD in eight dogs). Comparison of individual data shows that only 5.6 and 8.9% of the initial dose had been absorbed by the epidural veins after 2 hr in two of eight dogs. In the six remaining dogs, cumulative percentages ranged from 41.4 to 100% after 2 hr.

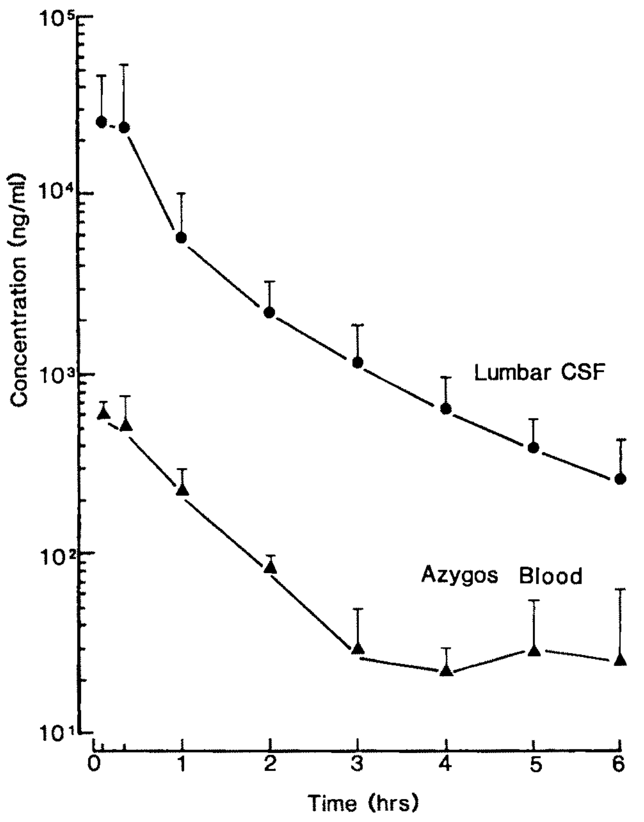

Figure 4. Log concentration–time curves in lumbar CSF and azygos vein after lumbar epidural injection of morphine (2 mg). During the first 3 hr, the rate of elimination of morphine from CSF and azygos blood does not differ. Mean ± SD of three dogs (numbers 2, 6, 7 in Tables 1 and 2).

Discussion

Epidural Catheterization

The approach of the epidural space described in this paper is comparable to the caudal approach in humans. In contrast to humans, the epidural catheter in the dog travels upward for 13 cm or more in a predictable direction along the axis of the spinal canal. The small amount of epidural fat in the dog, the size and orientation of the intervertebral foramina, and the relative rigidity of the catheter may explain the high success rate of insertion of long catheters. The same approach can be used for catheterization of the upper thoracic and cervical epidural space. However, the progression of the catheter should be followed

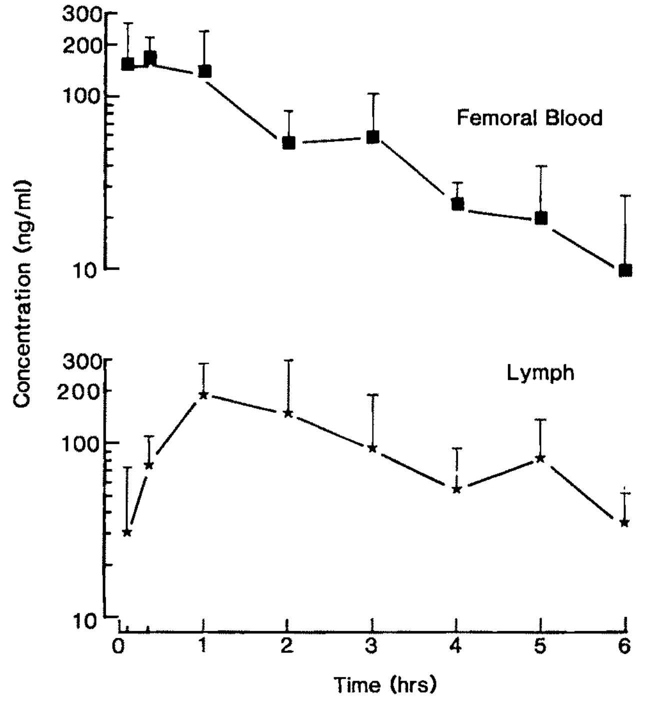

Figure 5. Log concentration–time curves in femoral artery and thoracic duct (lymph) after lumbar epidural injection of morphine (2 mg). Mean ± SD of three dogs (numbers 2, 6, 7 on Tables 1 and 2).

under fluoroscopy because of the smaller size of the vertebral canal at those levels (5).

Diffusion Across the Dura

In the dog model, morphine peaks in the lumbar CSF after 5 min (range: 5–60 min), while in humans such peaks have been reported after about 2 hr (range: 30 min–4 hr) (9–12). Furthermore, normalized to 1 mg of morphine injected epidurally, the mean morphine peak CSF level is 15.8 μg/ml in dogs and between 0.3 and 1.4 μg/ml in humans (9,11,13,14). The lower and more delayed peak CSF level in humans suggests that the dura represents a more significant barrier in humans than in dog. In the rat, the very thin dura does not seem to represent a significant barrier to narcotics (15). Thus the discrepancies among species in the diffusion process across the dura in vivo may be due to differences in dural thickness. Using cadaver dura, the transdural diffusion of drugs has been reported to vary inversely with the square root of molecular weight (MW) (16). In contrast, in the present in vivo studies, inulin (MW: 5175) and morphine (MW of monomer: 334) have comparable kinetic profiles in all compartments including the CSF after the epidural injection of both agents in the same animal. Indeed, the morphine/inulin AUC ratio in CSF was 0.39, suggesting that if anything inulin effectively crosses into the CSF more readily than morphine. This in vivo observation, which is in marked contrast to the in vitro modeling, should be confirmed in a larger group of animals.

The epidural/intrathecal (EPI/IT) AUC ratio represents the CSF bioavailability or the fraction of the epidural dose crossing the dura. Epidural injection of both morphine and inulin in one dog showed that 0.31% of morphine and 0.59% of inulin crossed the dura. Considering the wide variations in CSF disposition after epidural injection, these values should be interpreted with caution. Nevertheless, a 2% bioavailability has been reported in humans (17). In that study, CSF was considered as a one-compartment model and the AUCs were calculated between 10 and 25 hr after injection. Therefore, the initial elimination phase during which the IT–EPI differences are the largest was likely missed. In view of the short $t_{1/2}$-α values, the error resulting from this approximation should be minimal. However, as mentioned above, morphine CSF peak levels are about 15 times higher in dogs than in humans per mg of morphine injected epidurally, suggesting that the bioavailability is significantly lower in humans than in dogs. Therefore, a 2% bioavailability in humans probably is an overestimation. If the bioavailability in humans is estimated at between 0.1 and 1%, then the amount of morphine reaching the CSF should be at most between 1 and 10 μg per mg of morphine injected epidurally. Significantly, Nordberg and colleagues have shown with intrathecal morphine that the minimum effective analgesic dose in humans appears to be in the range of 250 μg, whereas the epidural dose is in the range of 5 mg. The apparent discrepancy between the magnitude of analgesia and the relatively small amount of morphine crossing the dura into the CSF after epidural injection emphasizes that CSF levels do not necessarily reflect the amount of drug which penetrates the parenchyma to bind to the receptors within the spinal gray matter. Other roads to spinal receptors such as the posterior radicular branch of the spinal segmental arteries may be necessary to explain the redistribution of epidurally injected drugs (18). This discrepancy between apparent CSF levels and analgesia after epidural injection is probably accentuated with hydrophilic agents (such as morphine) which diffuse relatively poorly through neural tissue (19).

Drug Clearance from CSF

After intrathecal (IT) injections of morphine (3 mg) in dogs, reported mean $t_{1/2}$-α and $t_{1/2}$-β values are 9.4 min and 116.7 min, respectively (20). These values are very

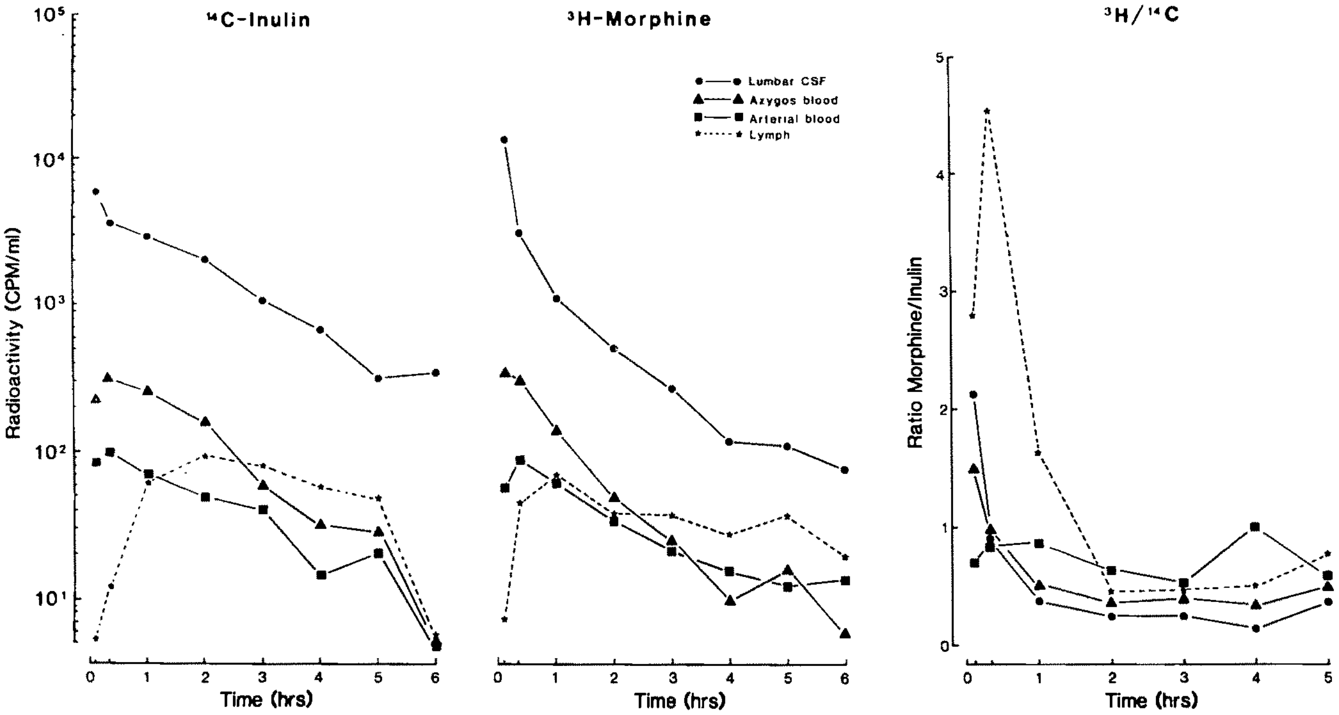

Figure 6. Radioactivity (CPM/ml) in the lumbar CSF, azygos vein, femoral artery, and thoracic duct after epidural injection of ^{14}C-inulin (left panel) and ^{3}H-morphine (middle panel) in one animal (number 7 on Tables 1 and 2). Data points were normalized to 10^6 CPM of injectate. The right panel shows the morphine/inulin ratio as a function of time.

close to that reported in this study after epidural (EPI) injection: 14.7 min and 106 min, respectively. In humans, after IT injection of morphine (2.5 mg), $t_{1/2}$-α values range from 0.21 to 1.4 min (21). In humans, reported mean $t_{1/2}$-β values are 175 min (IT, 0.25 mg) (12), 196 min (IT, 0.5 mg) (12), or vary from 107 to 239 min (EPI, 3–6 mg) (9,11,13) or from 14.8 to 363 min (IT, 2.5 mg) (21). These data suggest that $t_{1/2}$-α values are shorter and $t_{1/2}$-β values longer in humans than in dogs. In addition $t_{1/2}$-alpha and $t_{1/2}$-β values in the CSF appear to be independent of the dose and the route of administration (EPI versus IT).

It is interesting to compare morphine clearance from CSF with an agent, such as inulin, that does not undergo metabolism and does not cross cell membranes. In this study, the morphine/inulin AUC ratio in the CSF was 0.73 after IT injection. In monkeys, the β-endorphin/inulin AUC ratio in CSF after IT injection ranges between 0.74 and 1.0 (22). Therefore, morphine and β-endorphin appear to be cleared at a rate similar to that of inulin.

Drug Removal by the Epidural Veins

After epidural injection of morphine, drug levels in the azygos vein peaked at 5 min and were significantly greater than in the peripheral blood during the first 20 min. Comparable data were reported after epidural injection of mepivacaine in dogs (4). However, normalized to 1 mg of injectate, the peak levels in the azygos vein are about 5 times greater for morphine than for mepivacaine. In addition, it is reported that 9% of epidurally injected mepivacaine is recovered from the azygos vein in an hour (4). In our study, 49.2% of epidurally injected morphine was recovered in an hour (Table 2). Considering the small but discrete tissue uptake of morphine, such an estimate is conservative, because arterial levels subtracted from concurrently sampled azygos levels are somewhat greater than peripheral venous levels. The morphine–mepivacaine difference in removal by epidural veins can be explained by the physicochemical properties of the agents. Mepivacaine oil:water solubility ratio is 7:1 at pH 7.4. Therefore, 86% of mepivacaine was esimtated to be partitioned in the epidural fat and released slowly (4). Morphine oil:water solubility ratio is 1.4:1. Thus 29% of morphine should be partitioned in the epidural fat, and 71% should be available for transural diffusion and vascular absorption.

Comparison of Tables 1 and 2 shows that the wide variations in CSF kinetics cannot be explained by concurrent variations in azygos vein distribution. For instance, dog numbers 4 and 6 displayed comparable CSF kinetics and very different azygos vein distribution. Furthermore, Table 2 shows that the amount of drug recovered from the azygos vein is significantly lower in two dogs (numbers 3 and 4). Because the azygos catheters were appropriately situated at necropsy, it appears unlikely that the lower levels may have reflected systemic venous sampling. This raises the issue that as yet unidentified factors influence the redistribution into CSF and lymph.

Furthermore, Figure 6 shows that after epidural injection inulin and morphine levels in the azygos vein are comparable. This observation is in accordance with the rapid passage across capillary walls of all molecules with a MW up to 5000, whether ionized or nonionized, after intramuscular or subcutaneous injection (8).

Distribution in Arterial Blood

The significantly higher arterial levels of morphine during the first 60 min are probably due to the systemic redistribution after absorption of the drug by the epidural venous plexus.

Distribution in Lymph

India ink injection in the subarachnoid space of the rabbit produces filling of the lymph nodes anterior to the thoracic and lumbar vertebrae (23,24). Likewise, drainage of labeled albumin from cerebral interstitial fluid into deep cervical lymph nodes has been demonstrated in rabbits (25). In rats, epidurally injected methylene blue colors the lumbar prevertebral lymphatic channels and nodes (unpublished observations). Epidurally injected drugs may potentially enter the lymphatic system by three different routes: 1) by diffusion into the dural lymphatic vessels located at the level of the nerve roots; 2) by leakage out of the vertebral canal through the intervertebral foramina; and 3) by vascular absorption and systemic redistribution. Our study shows that the lymph levels of morphine after epidural injection were not different from the arterial levels. This observation suggests that lymph levels reflect systemic redistribution. In addition, after epidural injection of inulin and morphine in the same dog, lymph levels of both agents were comparable, except that morphine peaked at 1 hr and inulin at 2 hr (Fig. 6). This observation should be confirmed in a larger group of animals. In conclusion, while lymph appears to play a minimal role in the overall kinetics of epidurally injected morphine, it is likely that more lipid soluble agents such as fentanyl may be more prone to such redistribution.

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ANESTH ANALG
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Response of Left Ventricular Ejection Fraction to Recovery from General Anesthesia:

Measurement by Gated Radionuclide Angiography

P. Coriat, MD, O. Mundler, MD, D. Bousseau, MD, M. Fauchet, MD, A. C. Rous, E. Echter, MD, and P. Viars, MD

CORIAT P, MUNDLER O, BOUSSEAU D, FAUCHET M, ROUS AC, ECHTER E, VIARS P. Response of left ventricular ejection fraction to recovery from general anesthesia: measurement by gated radionuclide angiography. Anesth Analg 1986;65:593–600.

To test the hypothesis that, after anesthesia for noncardiac surgical procedures, the increased cardiac work during recovery induces wall motion and ejection fraction (EF) abnormalities in patients with mild angina pectoris, gated radionuclide angiography was performed in patients undergoing simple cholecystectomy under narcotic–relaxant general anesthesia. The ejection fraction was determined during anesthesia at the end of surgery, and then determined 3 min and 3 hr after extubation. A new angiography was performed 24 hr later, and a myocardial scintigraphy (Thallium 201) was performed during infusion of the coronary vasodilator, dipyridamole. In the first part of the investigation, eight patients without coronary artery disease (CAD) (group 1) and 20 patients with mild angina (group 2) were studied. In the second part of the study, seven patients (group 3) with mild angina pectoris received an intravenous infusion of 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of nitroglycerin started before surgery and gradually decreased 4 hr after extubation. In group 1, EF remained unchanged at recovery. In contrast in group 2, EF responded abnormally to recovery: EF decreased from 55% during anesthesia to 45% 3 min after extubation ($P < 0.001$). Patients in group 3, who received intravenous nitroglycerin, showed no change of EF at recovery. This study demonstrates that recovery from general anesthesia causes abnormalities in left ventricular function in patients suffering from CAD. These abnormalities are prevented by prophylactic intravenous nitroglycerin.

Key Words: RECOVERY—myocardial function. HEART—myocardial function.

Recovery from general anesthesia is associated with increased sympathetic nervous system discharge (1), and increases in heart rate, blood pressure, and global oxygen consumption. Increased cardiac work resulting from these changes has been previously documented (2). However, the effects of increased cardiac work on left ventricular function during recovery from anesthesia are, as yet, little known in patients with coronary artery disease. Nuclear medicine has made an important contribution to the assessment of global and regional left ventricular function. Equilibrium radionuclide angiography is a noninvasive, accurate, and reproducible technique, especially suited to the taking of repeated measurements (3,4). For these reasons, this technique is generally applied to the evaluation of left ventricular function during stress (5).

The purpose of this study was to test the hypothesis that recovery from anesthesia for noncardiac surgical procedures induces abnormalities of wall motion and of ejection fraction (EF). Radionuclide angiography was used to assess left ventricular EF and regional wall motion during anesthesia and anesthetic recovery in patients with and without coronary artery disease (CAD). Because several previous studies (6,7) have already demonstrated the beneficial effects of nitroglycerin on ventricular function during exercise, we also studied the effects of prophylactic intravenous nitroglycerin infusion on myocardial function during anesthetic recovery in surgical patients with mild angina pectoris.

Materials and Methods

We studied patients undergoing simple cholecystectomy lasting–3 hr. We chose this procedure because it is one of the most frequently performed in abdom-

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Some of the results of this study were presented at the ASA meeting, 1984.

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Address correspondence to Dr. Coriat, Department of Anesthesiology, Hôpital de la Pitié, Boulevard de l'Hôpital, 75013 Paris, France.

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Table 1. Patient Characteristics

	Group 1 (n = 8)	Group 2 (n = 20)	Group 3 (n = 7)
Age (yr)	65 ± 10	65 ± 13	60 ± 8
Duration of procedure (min)[a]	130 ± 15	126 ± 18	143 ± 19
Duration of anesthesia (min)[a]	160 ± 17	160 ± 17	174 ± 17
Previous inferior myocardial infarction[b]	—	4	2
Organic nitrates	—	10	3
β-Blockers[c]	—	6	2

Group 1, patients with CAD; group 2, patients with CAD; group 3, patients with CAD who were treated with nitroglycerin.

[a] Values are mean ± SD.

[b] Dating for more than 1 yr.

[c] Propranolol or acebutolol.

inal surgery, because it does not necessitate blood transfusion or the infusion of large volumes of fluid, and because the duration of operation varies little. In addition, patients are generally extubated at the end of surgery. Informed consent was obtained from each patient, and the protocol was approved by our ethics committee.

Study Patients

In the first part of the study, 28 patients, divided into two groups, were studied.

Patients without Coronary Artery Disease

Group 1 included eight patients without CAD, four men, and four women aged 55–77 yr, who were selected for cholecystectomy. These subjects had normal chest radiographs, physical examinations, and electrocardiograms at rest. Questioning elicited no symptoms suggesting CAD or pulmonary disease. None had hypertension or were taking any drugs.

Patients with Coronary Artery Disease

Group 2 consisted of 20 patients with a clear history of mild angina pectoris. Such angina occurred only with prolonged effort, or resulted in only slight limitation of ordinary activity. Patients in group 2 could climb more than one flight of stairs without chest pain.

We excluded the following patients from the study: 1) patients with hypertension; 2) patients receiving cardiac medications other than nitrates and short-acting β-blockers (propranolol, acebutolol); 3) patients suffering from disabling angina, or who had experienced chest pain in the 2 months before surgery, because such patients are particularly prone to developing peri- or postoperative episodes of ischemia with ST segment depression (8); 4) patients with a history of congestive heart failure, a cardiothoracic ratio greater than 55% on preoperative chest x-ray film, or an antecedent anterior or lateral myocardial infarction; 5) patients with supraventricular or ventricular arrhythmias that may perturb analysis of the radionuclide angiography; and 6) patients with left bundle branch block or left ventricular hypertrophy that renders interpretation of the ST segment difficult. Two patients who should have been included in group 2 experienced an ischemic-type ST segment depression during anesthesia. Because nitroglycerin was administered to treat these episodes, these two patients could not be included in our study.

In the second part of the study, seven additional patients with mild angina pectoris, who presented none of the criteria for exclusion determined for group 2, were assigned to group 3 and received an infusion of nitroglycerin during the period of the operation. The three groups were similar in age, duration of the surgical procedure, and clinical variables (Table 1).

Operative and Postoperative Protocol

Anesthetic procedure. The anesthetic procedure was identical for the three groups. Because the angina suffered by some of the patients was only mild, treatment was withheld beginning at midnight the night before surgery. Premedication, given 30 min before the operation, included intramuscular diazepam, 0.25 mg/kg, and atropine, 0.007 mg/kg. Anesthesia was induced by fentanyl, 3 μg/kg, with increments of thiopental and pancuronium. Ventilation was controlled throughout anesthesia with 60% N_2O in oxygen. Patients received further fentanyl, pancuronium, or thiopental when warranted.

Perioperative fluid administration was at the discretion of the anesthesiologist. The temperature of the operative room was maintained between 18 and 20°C.

In the second part of the study, the seven patients who were assigned to group 3 received an intravenous infusion of 0.4 μg/kg of nitroglycerin by means of a separate intravenous delivery system (shown in vitro to be nonabsorptive for nitroglycerin). Upon arrival in the operating room 300 ml of crystalloid were infused over 10 min, and NTG infusion was started before induction, gradually decreasing until termination 4 hr after extubation. Neither neuromuscular nor narcotic antagonists were administered at the end of the procedure. A long-term Holter ECG recording of lead V_5 and a good oscilloscopic trace V_5 were used in all patients to detect intra- and postoperative myocardial ischemia.

Radionuclide Angiography

The method of radionuclide angiography consists of two parts: first pass and equilibrium studies. All data were stored on magnetic disks and subsequently transferred to magnetic tapes for permanent storage.

First Pass Angiocardiography

Imaging was accomplished using a scintillation Anger camera equipped with a general purpose, low-energy, parallel hole collimator oriented in a left anterior oblique projection (30°), and adjusted to optimize separation of the left ventricular cavities from surrounding structures. A bolus of 15 mCi of 99 m pertechnetate-labeled autologous red blood cells (labeled in vitro) was injected through an antecubital vein to the supine patient. Scintigraphic data were collected and stored by an on-line computer (Intertechnique Cine 200). Each image frame had a spatial resolution of 64 × 64 matrix elements, and the framing rates were 200 frames/0.15 sec (corresponding to about 5 × 10 counts) for 30 sec. Left ventricular EF was computed by left ventricular time activity curves analysis obtained in the region of interest with the background activity previously subtracted using the Vandyke algorithm, according to the following formula where ED = end-diastolic and ES = end-systolic.

$$\mathrm{EF} = \frac{\text{ED counts} - \text{ES counts}}{\text{ED counts}}$$

Equilibrium Gated Radionuclide Ventriculography

After the radionuclide had equilibrated with the circulating blood volume (5 min), 1 million counts (approximately 250 cardiac cycles) were acquired in list mode on magnetic tape by the computer. The temporal resolution was obtained by gating the registered activity from the ECG in 12 frames per cardiac cycle (cardiac cycles shorter than 80% of the average length were excluded from analysis). The functional images of amplitude and phase were then obtained by Fourier analysis of the scintigraphic data. The digital images were displayed in a 64 × 64 matrix on a video screen and sequentially viewed. The images permitted an accurate determination of the left ventricule valvular plane, and selection of the end-diastolic and end-systolic frames. Using a light pen, a region of interest was then manually traced around the left ventricle in these two frames. The global left ventricular EF was determined from the formula displayed previously.

To define the background, we developed an automated computer algorithm: the global EF (GEF) that we determined during the first pass study with background correction (Vandyke) was different from that determined during the equilibrium gated radionuclide ventriculography without background correction as a standard condition. Because the two measurements must be the same, we concluded that the importance of the background made them different. Thus the ratio of the first pass EF to the equilibrium studies EF gave a coefficient that reflected the effect of these backgrounds, and we corrected the EF equilibrium background by means of this coefficient.

Regional Ejection Fraction

The same resulting left ventricular regions of interest were subdivided into 16 equiangular sectors around their center of mass, and the sectorial EF (SEF) was obtained in each sector from the same formula. Only 12 of the 16 equiangular sectors were considered, because four segments concerning the valvular plane were eliminated. With the left anterior oblique incidence (30°/15°) used in this study, sectors were attributed to myocardial septal (four sectors), apical inferior (four sectors), and lateral areas (four sectors). All equilibrium studies were interpreted by two physicians with experience in this technique who were aware of the patients' clinical statuses. Measurements were repeated twice by each physician, and the mean results were retained. Measurements obtained in our laboratory from 33 subjects without cardiovascular or pulmonary artery disease established the normal values for left ventricular EF (66 ± 7, mean ± SD) and the mean normal SEF for each sector. Standke et al. (9) have pointed out that, when comparing an individual SEF profile with the mean normal SEF, the dependence of the mean normal SEF on the GEF of the patients considered must be taken into account. Thus mean normal SEF was adjusted to the individual left ventricle by normalizing to the individual GEF according to the following formula (9):

Table 2. Systolic Blood Pressure and Heart Rate before, during, and after Operation

	Preoperative	Anesthesia[a] (T1)	3 Min after extubation (T2)	3 Hr after extubation (T3)	24 Hr after surgery (T4)
Systolic blood pressure (mm Hg)					
Group 1	138 ± 13	125 ± 18	149 ± 20	143 ± 19	134 ± 17
Group 2	148 ± 14	135 ± 15	156 ± 17	150 ± 17	148 ± 13
Group 3	143 ± 10	122 ± 9	140 ± 8	137 ± 8	143 ± 9
Heart rate (beats/min)					
Group 1	77 ± 7	72 ± 9	102 ± 10	100 ± 9	75 ± 8
Group 2	81 ± 8	77 ± 9	107 ± 12	97 ± 9	79 ± 8
Group 3	75 ± 7	85 ± 8	99 ± 7	97 ± 7	78 ± 7

[a] N_2O, 60%, in oxygen.
Groups described in Table 1.

$$\text{Adjusted normal SEF} = \frac{\text{mean normal SEF} \times \text{GEF}}{0.66}$$

In this equation 0.66 represents the normal GEF.

This adjusted normal SEF profile permits the determination of hypokinetic sectors defined as sectors with an adjusted SEF lower by two standard deviations than the adjusted normal SEF. At each angiographic measurement, adjusted SEFs were determined in the 12 sectors considered, and these SEFs were compared to the adjusted normal SEF.

Labeled red blood cells were injected immediately at the end of the surgical procedure, and the first measurements (T1) were made under controlled ventilation with 60% N_2O in oxygen while patients were still in an unresponsive state. To assess possible changes in EF because of mechanical ventilation in group 2, in the first six patients of this group a measurement was made just after T1, while N_2O in oxygen was administered by gently compressing the reservoir bag every 15 sec during the data acquisition. There was less than ±7% change in EF between these two points. After N_2O in oxygen patients breathed 100% oxygen spontaneously or, when respiration was insufficient, by gentle compression of the reservoir bag. The trachea were extubated when patients could open their eyes on command, when the respiratory rate reached 12 breaths/min and the tidal volume 8 ml/kg, and when a sustained head lift could be obtained. Measurements were repeated 3 min (T2) and 3 hr (T3) after extubation. The interval between T1 and T2 was 8–10 min. Twenty-four hours later, labeled red blood cells were injected, and new equilibrium radionuclide angiographic study was performed (T4).

No preoperative measurements of EF could be performed in the framework of this study 1) because patients' suffering from mild angina pectoris were admitted to our surgical unit 24 hr before the procedure, making it impossible for us to schedule preoperative radionuclide imaging; and 2) the 35 patients included in this study were operated on by the same two surgeons, and we did not wish to inject technetium 99 m in all patients prior to surgery.

Thallium 201 Myocardial Scintigraphy under Dipyridamole

The scintigraphic examination was performed 24–48 hr after surgery in all patients: 2 mCi of thallium 201 was administered intravenously after a 4-min infusion of the coronary vasodilator dipyridamole, 0.14 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$ (10,11). Data were collected with the same camera that was used for angiography, now set for 80 ± 8 keV, with an additional circular collimator (diameter, 20 cm). Data were interpreted by two independent observers who were unaware of patients' clinical statuses. Myocardial imaging was performed 5 min after administration of the thallium and was not repeated later.

Images were obtained in four subsequent views: anterior (30°/15° and 45°/20°), left anterior oblique, and left lateral. The minimum number of counts collected in each view was 2 million. Data were recorded on film directly from the cathode ray display and were stored in the histogram as 64 × 64 digitalized images. The digitalized images were further processed on an Intertechnique Cine 200 computer.

Processing was designed to minimize the influence of variable backgrounds: 1) the images were subjected to a nine-point weighted smoothing; 2) net myocardial activity was determined from the peak counts of multiple-count profiles generated across the myocardial images after subtraction of the background reference plane. Both film and computer processed data were used in the interpretation. The four views

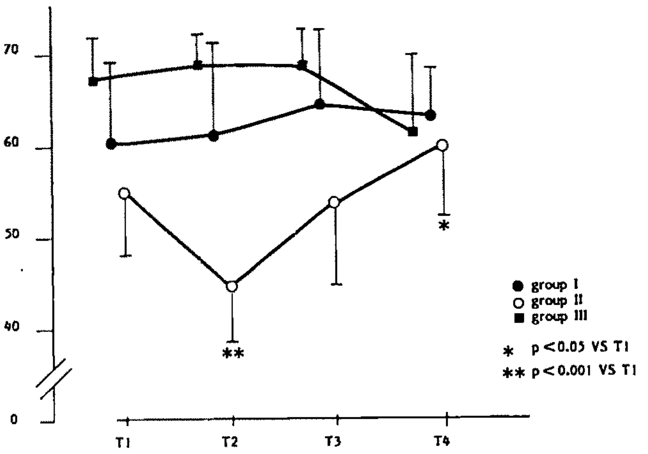

Figure 1. Effect of recovery on left ventricular function as determined by ejection fraction (EF) (mean ± SD) in patients without CAD (Group 1), in patients with CAD (Group 2), and in patients with CAD receiving nitroglycerin infusion (Group 3). Measurement times are defined as follows: T1, during anesthesia (N_2O, 60%, in oxygen); T2, 3 min after extubation; T3, 3 hours after extubation; and T4, 24 hr after anesthesia.

permitted precise analysis of the five sectors of the left myocardium: anteroseptal, apical, inferior, basal, and lateral.

Results

All the patients in this study had normal uncomplicated postoperative courses. Continuous monitoring of the ECG did not reveal any ischemic episodes in the patients studied. Rectal temperature, measured at the end of anesthesia, was between 35.4 and 36.0°C.

Postoperative thallium 201 scintigraphy with dipyridamole infusion was normal in group 1 (control subjects), but revealed ischemic image defects in groups 2 and 3. In these two groups, ischemic defects were located in the lateral segment in 10 patients, the anteroseptal in 3, the apical in 2, the inferior in 6, and both the apical and lateral segments in 6.

Four sets of radionuclide angiographic measurements were obtained: at the end of the surgical procedure in unresponsive patients under controlled ventilation with N_2O in oxygen (T1), 3 min (T2) and 3 hr (T3) after extubation, and 24 hr later (T4). There was no significant difference between groups 1 and 2 in heart rate and systolic blood pressure measured by sphygmomanometry before surgery and when radionuclide measurements were made at T1, T2, T3, and T4 (Table 2). In group 1, EF remained unchanged at T1, T2, T3, and T4 (Fig. 1). In group 2, EF responded abnormally to recovery, and an obvious decrease appeared at T2 in relation to T1, EF decreased from 55 ± 7% to 45 ± 7% (Fig. 1). Furthermore, global EF in group 2 at T4 was greater than at T1 (60 ± 8% vs 55 ± 7%). Systolic blood pressure was lower at T1 and T2 in groups 2 and 3 (Table 2). In contrast to group 2, no decrease in EF was noted between T1 and T2 in group 3 (Fig. 1).

Regional Left Ventricular Function

In the three groups, the presence of hypokinetic sectors was looked for at T1, T2, and T4 in each of the 12 sectors analyzed by radionuclide ventriculography. The number of hypokinetic sectors and their localization in regard to myocardial segments in which an image defect was located during thallium 201 scintigraphy under dipyridamole are given in Table 3. In three patients in group 2, one or two sectors that were not hypokinetic at T1 became hypokinetic at T2. All these sectors were located in areas with decreased thallium uptake.

Statistical Analysis

Results are expressed as mean ± SD and were analyzed using variance analysis with Newman–Keuls test.

Discussion

On recovery from general anesthesia performed for noncardiac surgical procedures, several factors summate to provoke tachycardia, preload and afterload stress, and increased global oxygen comsumption (2). The factors responsible for these changes are rewarming stress, hypoxia, emergence excitement, postoperative pain, and the passage going from assisted to spontaneous ventilation. Increases in heart rate (25%), left ventricular stroke work index (55%), and mean blood pressure (30%) were noted just after spontaneous recovery in patients without CAD.

To ensure safe management during the immediate postoperative period of patients suffering from CAD, knowledge of the response of left ventricular function to this stressful situation is important. In this study, equilibrium radionuclide angiography was used to assess global and regional left ventricular function during recovery. Quantitative analysis of sequential count densities of gated or first pass blood pool images provides a highly reproducible and accurate measure of left ventricular GEF (3–5). The validity and reproducibility of measurements of GEF by means of this technique have been well documented (3–5, 12). The intra- and interobserver variability in our laboratory, the same as that reported in several other studies (4,5,12), had a standard deviation of 4–6 EF units (%).

Several recommended measures for ensuring the

Table 3. Number of Hypokinetic Sectors in Patients of the Three Groups

	Patients with at least one hypokinetic sector	Number of hypokinetic sectors	
		In areas with thallium defect	In areas with normal thallium uptake
Group 1 (n = 8)			
T1	0	0	0
T2	0	0	0
T4	1	0	1
Group 2 (n = 20)			
T1	9	22	7
T2	7	19	2
T4	5	6	2
Group 3 (n = 7)			
T1	0	0	0
T2	0	0	0
T4	2	3	0

Groups described in Table 1.

best reproducibility of measurements (4) have been used in this study. Each measurement was made twice by two physicians fully experienced in this technique, and the total number of counts collected was the same at each point. The possible inaccuracy caused by changes in the positions of patients was minimal in our study because the patients remained in the same position during recovery.

When using gated radionuclide angiography, regional EF can be measured from sequential changes in count density in segments of a radionuclide angiogram (9, 13–15). We used this approach to assess quantitatively left ventricular wall motion by means of regionally derived radionuclide EF. However, measurements obtained by this approach, even though they have an excellent reproducibility, have not been well-confirmed by independent measures of regional function, which explains why the validity of quantitative measurements of regional function using gated blood pool imaging is less well-established than the validity of GEF. When the radionuclide ventriculogram is used to assess left ventricular wall motion, only major abnormalities, such as akinesia, are readily detectable. In order to be able to confirm the occurrence of hypokinesia in a sector using an SEF profile, the SEF must be adjusted to the individual left ventricle. Effectively, enlarged left ventricular end-diastolic volume involves a decreased GEF as well as a diminished SEF profile, although the contraction amplitude remains constant (9).

We studied only patients with mild angina pectoris and without other cardiac disease, who had not experienced ST segment depression preoperatively, because such patients are generally extubated at the end of a cholecystectomy. In a previous study at our institution (16), comparison of both pre- and postoperative thallium 201 dipyridamole scintigrams and radionuclide angiography revealed the development during the operative period of disturbances of metabolic and functional properties of myocardial segments only in patients who experienced intraoperative ischemic episodes detected by continuous ECG recording. In this previous study, in the 14 out of 20 patients included who did not experience either intra- or postoperative ST segment depression, no changes in EF and no new wall motion abnormalities were detected at the time of postoperative radionuclide angiography.

In groups 2 and 3, the near-normal value of EF determined 24 hr after surgery and the lack of ischemic episodes with ST segment depression are accounted for by the criteria of selection of the patients studied. The lack of ST segment depression during recovery is not surprising because ST segment depression generally occurs during the immediate postoperative period, particularly in patients suffering from disabling angina (8) or in patients who experienced perioperative ST segment depression.

Postoperatively thallium 201 imaging was obtained after the infusion of dipyridamole, a coronary vasodilator (10,11), to confirm any myocardial perfusion abnormalities of patients included in groups 2 and 3. This noninvasive technique permits detection of coronary artery stenoses without inducing functional ischemia (11). All patients with CAD included in these groups had defects with thallium–dipyridamole imaging. The remarkably good sensitivity is not surprising, because a sensitivity of 93% has been reported by different authors (5, 10, 11). Because thallium scintigraphy was performed postoperatively, it may be possible that some perfusion deficit noted in patients with CAD could be due to a prolonged alteration in the metabolic state of the myocardium caused by anesthesia or surgery (20).

The main result of this study demonstrates that immediately after extubation the left ventricular EF decreased significantly in patients suffering from mild angina pectoris. These changes in ventricular performance, which occurred in the absence of ischemic electrocardiographic abnormalities, may indicate either altered ventricular reserve as a result of increased afterload, preload, or heart rate, or an imbalance in the oxygen supply and demand relationship. Alteration in global and regional left ventricular function during exercise and modifications in heart rate and loading conditions have been the subject of numerous investigations (7, 21–23). These studies indicate that decreased EF is a complex response influenced by several variables such as resting pulse pressure, adequate exercise, resting EF, exercise ECG changes, and the severity of the CAD. In CAD, Giles et al. demonstrated that, after tracheal intubation, left ventricular EF estimated by the nuclear stethoscope is decreased (24).

The fact that fewer sectors were hypokinetic at T2 than at T1 in group 2, although GEF decreased, is consistent with altered ventricular reserve after alterations in preload or afterload and changes in heart rate in the absence of ischemia. Although no patients had ST segment changes or chest pain indicating ischemia, an imbalance in the oxygen supply and demand relationship leading to a decrease in functional properties of myocardial segments may have played a part in the decrease in EF. As we had foreseen, analysis of SEF profile does not permit demonstration of the development of segmental wall-motion abnormalities as well as echocardiography does (25). Such abnormalities are sensitive and specific markers of regional ischemia (17,18). They occur within seconds of regional lactate production, even when only the subendocardium is affected, and before or in the absence of changes on the ECG (17,18). During exercise testing, electrical changes in ventricular myocardium occur at a higher ischemic threshold than contractile changes (21,22). Using two-dimensional transesophageal echocardiography, Smith et al. (19) demonstrated that intraoperatively, new segmental wall motion abnormalities occurred four times more frequently than ST segment changes. In patients with disabling CAD, during induction of anesthesia tracheal intubation the occurrence of ventricular wall motion abnormalities has been documented using cardiokymography (26). In the coronary ischemic patients studied, EF was slightly but significantly lowered at the end of the surgical procedure, and an obvious decrease in EF occurred after extubation.

The marked decrease in EF noted after extubation is consistent with the hypothesis that the frequency and magnitude of the decrease in EF during recovery depends on the mass of potentially ischemic myocardium present at the end of the surgical procedure. During exercise testing, patients with normal resting left ventricular EF presented the greatest decrease in left ventricular EF and the highest frequency of new regional dysfunction (22).

The findings of the present study do not indicate why GEF is lower during anesthesia immediately after surgery than 24 hr after the operation. If we could have measured EF preoperatively, we could have evaluated this point more precisely. Theoretically, two mechanisms may play a part in explaining the decrease in EF at the end of surgery: during the operative period an imbalance between myocardial oxygen supply and demand may have occurred without producing ST segment depression. This situation may produce ventricular dysfunction lasting several hours (20). The other possibility is that N_2O has detrimental effects on areas of the myocardium supplied by a compromised coronary artery (27).

The beneficial effects of intravenous nitroglycerin administration in ischemic heart disease are well-known (28). In particular, nitroglycerin improves ventricular function at rest and during exercise (6,7). Variance analysis did not show any modification in EF at T1 and T2 in group 3, which indicates that the prophylactic nitroglycerin administered to group 3 prevented the decrease in EF noted after extubation. This effect is probably secondary to a decreased afterload stress and/or to an improvement in regional myocardial blood supply and oxygen demand leading to an increase in the functional properties of myocardial segments during recovery in patients receiving intravenous nitroglycerin infusion (28).

In conclusion, this study demonstrates that recovery from general anesthesia causes abnormalities in left ventricular function in patients suffering from mild angina pectoris. These abnormalities occur in the absence of ischemic ST segment depression detected by ECG recording. Thus, just after extubation in patients with CAD, the cardiac work and global oxygen consumption increase, but global and regional left ventricular function decrease. The prophylactic infusion of nitroglycerin prevents these changes. These facts permit better understanding of the physiopathology of some of the cardiac complications that threaten patients with CAD during the postoperative period.

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Spinal and Supraspinal Mechanisms for Morphine–Pentobarbital Antinociceptive Interaction in Relation to Cardiac Acceleration Response in Rats

John A. Jebeles, BS, Igor Kissin, MD, PhD, and Edwin L. Bradley Jr, PhD

JEBELES JA, KISSIN I, BRADLEY EL Jr. Spinal and supraspinal mechanisms for morphine–pentobarbital antinociceptive interaction in relation to cardiac acceleration response in rats. Anesth Analg 1986; 65:601–4.

In rat experiments, morphine–pentobarbital antinociceptive interaction affecting cardiac acceleration in response to somatic noxious stimulation was analyzed with the use of intrathecal and intracerebroventricular injections of morphine. Cardiac acceleration response was induced by tail compression, and heart rate was monitored by electrocardiogram. Pentobarbital, in a subanesthetic intravenous dose, antagonized the antinociceptive effect of morphine in relation to cardiac acceleration response when morphine was administered intracerebroventricularly. Without pentobarbital, morphine, 8 μg, almost completely blocked the cardiac acceleration response, which was only 1 ± 1 beats/min. When pentobarbital (10 mg/kg intravenously) was administered in a combination with the same dose of morphine, the cardiac acceleration response was 29 ± 3 beats/min ($P < 0.0001$). In contrast, when morphine was administered intrathecally, the antagonism by pentobarbital of the cardiac acceleration response was absent. The results suggest that supraspinal mechanisms play a decisive role in morphine–pentobarbital antagonism in relation to cardiac acceleration response to somatic noxious stimulation.

Key Words: ANALGESICS—morphine. HYPNOTICS, BARBITURATES—pentobarbital. PAIN—vascular responses.

In rat experiments, subanesthetic doses of intravenous pentobarbital previously have been found to antagonize the inhibitory effect of intravenous morphine on cardiac acceleration response to noxious stimulation (1). Antagonism with morphine in relation to cardiac acceleration response to noxious stimulation was also demonstrated when subanesthetic doses of halothane were used (2). The following explanation was suggested for the ability of pentobarbital and halothane to antagonize the effect of morphine on the heart rate response to noxious stimulation: The effect of morphine on the cardiac acceleration response results primarily from recruitment of some inhibitory control system concerned with this response. Pentobarbital or halothane depresses this system, and as a result, the effect of morphine on the cardiac acceleration response is profoundly weakened (1,3).

Antinociceptive effects of opioids may be a consequence of 1) passive blockade of nociceptive throughput at the spinal and supraspinal levels, and/or 2) recruitment of active inhibition of nociceptive throughput, also involving the supraspinal or spinal systems (4). Thus in theory, pentobarbital could antagonize the effect of morphine on cardiac acceleration response at both spinal and supraspinal levels. In the present study, we evaluated the extent to which spinal and supraspinal mechanisms contribute to the morphine–pentobarbital antagonism of the cardiac acceleration response to pain. The role of spinal and supraspinal suppression systems was analyzed with the use of intrathecal and intracerebroventricular injections of morphine.

Methods

Male Sprague–Dawley rats (300–350 g) with chronically implanted intrathecal or cerebroventricular catheters were used for the study ($n = 66$). Intrathecal catheters (PE 10) were implanted according to Yaksh and Rudy (5). Cerebroventricular catheters (PE 20) were implanted in the left lateral cerebral ventricle according to Brakkee et al. (6). The position of the catheter was verified after the experiment by the injection of India ink. Surgical procedures for implan-

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Address correspondence to Dr. Kissin, Department of Anesthesiology, University of Alabama at Birmingham, University Station, Birmingham, AL 35294.

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tation of the catheters were performed under halothane anesthesia (2%, inspired) 4 or 5 days before the experiments.

The experiments were carried out in a clear chamber 30 × 25 × 40 cm in size. The rat's tail (for noxious stimulation) or hind leg (for drug injections into the saphenous vein) could be extended from the chamber through a slot. Noxious stimulation was produced by compression of the tail (1 kg on a 0.25-cm^2 area in the middle of the tail) for 60 sec. Heart rate response to the noxious stimulation was monitored from an electrocardiogram. In order to obtain ECG recordings in unrestrained animals, chronic electrodes from insulated steel wire were inserted subcutaneously (7) simultaneously with the implantation of cerebroventricular or intrathecal catheters. Heart rate was monitored by a special microcomputer-based cardiotachometer that counted the number of beats during 15-sec time intervals with an output update every 5 sec (2). The cardiotachometer provided records of heart rate on a Grass 7-D polygraph. Maximal increase in the heart rate at the end of a 60-sec period of stimulation was used for statistical calculations.

Three series of experiments were performed. First, a pilot series of experiments was performed to find equipotent doses for intrathecal and intracerebroventricular morphine with regard to suppression of cardiac acceleration response to noxious stimulation. With intracerebroventricular morphine administration, 3-, 5-, and 8-μg doses were used with four animals receiving each dose level. With the intrathecal route, 10-, 15-, and 20-μg doses were administered, also four animals per dose.

A second series of experiments was performed with intracerebral administration of morphine (8 μg), using two groups of seven animals. In one group, morphine was administered with pentobarbital (10 mg/kg intravenously), in another (control) with saline (intravenous). The morphine dose was selected on the basis of the results obtained in the pilot series of experiments.

The third series of experiments involved the intrathecal administration of morphine; this series also used one group of animals with pentobarbital (10 mg/kg intravenous) and one without. Due to the nature of data to be obtained in this series of experiments (see Results), two subseries of experiments were performed: one with morphine, 15 μg (seven experiments with saline and seven with pentobarbital) and another with morphine, 20 μg (also seven experiments with saline and seven with pentobarbital).

Morphine (Merck Co.) was injected into a cerebroventricular or intrathecal catheter with a Hamilton syringe. The agent was dissolved in a balanced ion solution (5). Volume of injection was 10 μl. Pentobarbital (Butler Co.) was injected intravenously. Both agents were administered 15 min before the test of cardiac acceleration response. In all series of experiments, each animal was given only one dose of the agent or agents, and noxious stimulation was applied only once.

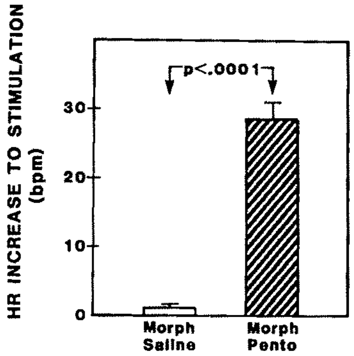

Figure 1. Interaction of intracerebroventricular morphine with pentobarbital regarding cardiac acceleration response to noxious stimulation. Columns represent mean ± SEM of determinations made in two groups of rats (seven animals in each group). Saline control group received morphine, 8 μg intracerebroventricularly; morphine–pentobarbital group received the same dose of morphine in combination with pentobarbital, 10 mg·kg^{-1}, intravenously. HR, heart rate.

Results are presented as the mean plus or minus SEM. The statistical significance of differences in the effect of morphine on cardiac acceleration response with and without pentobarbital as assessed by the two-sample *t*-test (8). A linear regression model relating cardiac acceleration response to log morphine doses (intrathecal and intracerebroventricular) was made by the method of least squares (9). These equations were used to estimate the potency ratio relating to intrathecal and intracerebroventricular routes of morphine administration (10).

To comply with institutional policy and standards of the American Association for Accreditation of Laboratory Animal Care, the cardiac acceleration response without administration of morphine was not tested. Values for cardiac acceleration response to noxious stimulation without analgesia were taken from our previous study where conditions of noxious stimulation were the same. (See reference 2, Fig. 2.)

Results

Figure 1 summarizes the effect of intracerebroventricular morphine on the cardiac acceleration response to noxious stimulation with and without pentobarbital. Without pentobarbital, morphine (8 μg) almost completely blocked the cardiac acceleration response (1 ± 1 beats/min). When pentobarbital (10 mg/kg in-

Table 1. Effect of Pentobarbital on Inhibition of Cardiac Acceleration Response to Noxious Stimulation Induced by Intrathecal Morphine

Morphine (μg)	Pentobarbital[a] (mg/kg)	*n*	Baseline heart rate (beats/min)	CA (beats/min)	*P*
15	0	7	442 ± 21[b]	23.1 ± 8.1	—
15	10	7	452 ± 9	18.1 ± 3.6	NS
20	0	7	458 ± 21	2.1 ± 1.1	—
20	10	7	463 ± 15	1.7 ± 0.9	NS

Abbreviations: CA, cardiac acceleration response to the tail compression; NS, not significant, as compared to the above group.

[a] Pentobarbital was administered intravenously.

[b] Mean ± SEM.

travenously) was administered in combination with the same dose of morphine, the cardiac acceleration response was 29 ± 3 beats/min ($P < 0.0001$). The difference indicates that pentobarbital weakens the effect of intracerebroventricular morphine on cardiac acceleration response. In contrast, as seen in Table 1, when morphine was administered intrathecally, the antagonism of pentobarbital regarding the cardiac acceleration response was absent. When morphine was used without pentobarbital (with saline) in a dose of 20 μg, it caused complete blockade of the cardiac acceleration response. A combination of the same dose of morphine with pentobarbital (10 mg/kg, intravenously) did not weaken the effect of morphine. To exclude the possibility of synergism between morphine and pentobarbital with this route of morphine administration, an additional subseries of experiments with morphine, 15 μg, was used. In this dose, morphine does not suppress the cardiac acceleration response completely, thus making it possible to find out whether a morphine–pentobarbital combination produces a more pronounced effect than morphine used alone. As seen in Table 1, the addition of pentobarbital did not cause significant changes in the effect of morphine on the cardiac acceleration response. Figure 2 represents linear regression models relating the cardiac acceleration response to the morphine dosage with intracerebroventricular and intrathecal routes of its administration. Data from the pilot series of experiments and from the two other series (experimental groups using morphine without pentobarbital) were used to generate these regression lines. Potency ratio relating intracerebroventricular and intrathecal morphine administration was 2.99, with 95% fiducial limits 1.81 and 5.01.

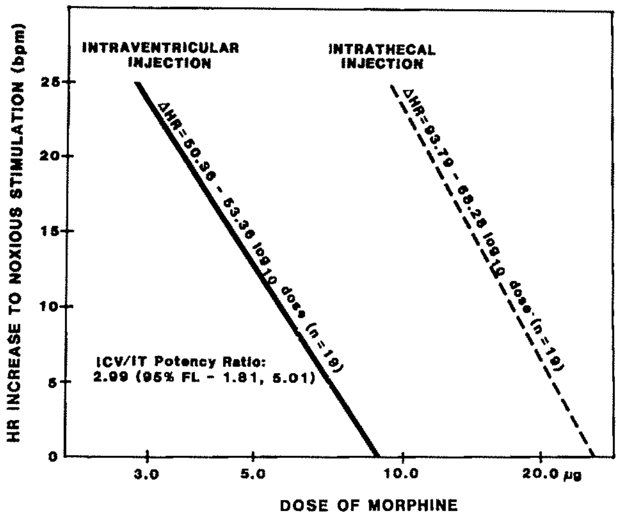

Figure 2. Linear regression models relating the cardiac acceleration response to the dose of morphine administered intracerebroventricularly and intrathecally. Abbreviations: ICV/IT, potency ratio relating intracerebroventricular and intrathecal morphine (see Methods section); FL, fiducial limits; HR, heart rate.

Discussion

The results of the present study show that morphine, whether used intracerebroventricularly or intrathecally, produces a dose-dependent suppression of cardiac acceleration response to somatic noxious stimulation. In rat experiments, somatic noxious stimulation has been found to result in a cardiac acceleration response that is accompanied by an increase in cardiac sympathetic nerve activity. Severance of the cardiac sympathetic and parasympathetic nerves has shown that the cardiac acceleration response to somatic noxious stimulation is mediated by cardiac sympathetic nerves without significant vagal contributions (11). Thus the index chosen for the present study represents a somatosympathetic reflex, and the ability of morphine to inhibit this reflex agrees with the report (12) that opioids markedly depress somatosympathetic C reflex recorded via the inferior cardiac nerve.

Antinociceptive effects of locally applied morphine may be due either to direct inhibition of nociceptive throughput or to recruitment of active inhibition of nociceptive pathways. These mechanisms may be involved on both the spinal and supraspinal levels (4). The present study demonstrates that morphine–pentobarbital antagonism in relation to cardiac acceleration response to noxious stimulation (1) may be reproduced with intracerebroventricular, but not intrathecal, administration of morphine. This fact suggests that the outcome of the morphine–pentobarbital interaction regarding cardiac acceleration response is determined at the supraspinal level.

Morphine–pentobarbital antagonism may be explained if we assume that the effect of morphine on the cardiac acceleration response is due to the recruitment of a supraspinal system inhibiting the nociceptive reflex: pentobarbital acts by suppressing the descending control mechanism recruited by morphine. Pentobarbital has been reported to abolish reticular inhibition (caused by electrical stimulation of bulbar reticular formation) of segmental reflex potentials (13). This fact agrees with the above suggestion, that in a similar way supraspinal inhibition activated by morphine may be suppressed by pentobarbital.

The alternative explanation for the morphine–pentobarbital antagonism may be based on Martin's hypothesis on pharmacologic redundancy as an adaptive mechanism in the central nervous system (14). He suggested that functional systems in the CNS are comprised of multiple subgroups of parallel pathways that differ from each other in that the types of serially organized neurons comprising them differ in their sensitivity to pharmacologic agents (morphine). Pentobarbital may disinhibit redundant pathways for the cardiac acceleration reflex that have a low sensitivity to morphine. As a result, somatic sympathetic reflex blocked by morphine reappears after administration of relatively small doses of pentobarbital.

In conclusion, our results suggest that supraspinal mechanisms play a predominant role in morphine–pentobarbital antagonism in relation to cardiac acceleration response to somatic noxious stimulation.

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Failure of Nalbuphine to Antagonize Morphine:
A Double-blind Comparison with Naloxone

Peter L. Bailey, MD, Norman J. Clark, MD, Nathan L. Pace, MD, Maria Isern, and Theodore H. Stanley, MD

BAILEY PL, CLARK NJ, PACE NL, ISERN M, STANLEY TH. Failure of nalbuphine to antagonize morphine: a double-blind comparison with naloxone. Anesth Analg 1986;65:605–11.

The authors studied the respiratory and analgesic effects of nalbuphine (0.21 mg/kg, intravenous), naloxone (0.014 mg/kg, intravenous), and placebo (normal saline) when given after morphine (0.21 mg/kg, intravenous) in a double-blind, randomized fashion. Resting end-tidal CO_2 ($P_{ET_{CO_2}}$), ventilatory and occlusion pressure responses to CO_2 rebreathing, and pain threshold were measured in 12 healthy adult volunteers before, 5 min, and 30 min after morphine. Nalbuphine, naloxone, or saline were administered 55 min after morphine, and the above measurements were repeated 5 min later (60 min after morphine) as well as 90, 120, 180, and 240 min after morphine. Whereas naloxone reversed respiratory depression as measured by all three respiratory parameters, nalbuphine either further depressed (resting $P_{ET_{CO_2}}$) or did not affect (ventilatory and occlusion pressure responses to CO_2 rebreathing) respiratory drive. Morphine produced a significant elevation of the pain threshold. Significant decreases in the pain threshold were seen only after naloxone. Saline and nalbuphine did not significantly alter the pain threshold. The data indicate that nalbuphine may not reliably antagonize moderate doses of morphine.

Key Words: ANALGESICS—morphine. ANTAGONISTS, NARCOTIC–nalbuphine.

Nalbuphine is an agonist/antagonist opioid with a "ceiling effect" that limits its respiratory depression and analgesia (1,2). Nalbuphine has also been used as an alternative to naloxone for the reversal of opioid-induced respiratory depression (3–7). Proposed advantages of nalbuphine as an opioid antagonist include a lower incidence of side effects (e.g., arrhythmias, hypertension), little chance of renarcotization, and sparing of analgesia and sedation. However, the effectiveness of nalbuphine as an opioid antagonist has not been evaluated in a carefully performed, double-blind comparison with naloxone. Also, although nalbuphine apparently does restore adequate ventilation after large doses of opioids used in anesthesia (4–7), whether or not nalbuphine reverses the effects of moderate doses of opioid agonists is not known. Therefore, the objectives of this study were to quantify in a double-blind, randomized fashion the respiratory and analgesic effects of nalbuphine and naloxone when given after morphine sulfate.

Methods and Materials

The protocol was approved by the Institutional Review Board at the University of Utah Health Sciences Center, and informed consent was obtained from 12 healthy (ASA I) adult volunteers. Each subject was tested at three sessions at least 48 hr apart. Study sessions began at 8:00 AM, and all subjects refrained from alcohol, caffeine, and aspirin for 24 hr and fasted for 8 hr prior to each session.

Upon arrival in the morning, subjects reclined in a dimly lit, quiet area. After local infiltration with 0.5 ml 1% lidocaine, an intravenous catheter was inserted into a peripheral vein and a 0.9% NaCl solution infused at 100 ml/hr. A CO_2 rebreathing challenge and a pain threshold determination were then performed to familiarize subjects with the tests and to allay anxiety. After a 15-min rest period, baseline resting end-tidal CO_2 ($P_{ET_{CO_2}}$), ventilatory and occlusion pressure responses to CO_2 rebreathing, and pain threshold were measured. Ten minutes later, 0.21 mg/kg of morphine sulfate was injected intravenously over 1 min. Five and 30 min after the injection of morphine, all evaluations were repeated. Fifty-five minutes after the injection of morphine, subjects received either nalbuphine (0.21 mg/kg), naloxone (14 μg/kg), or normal saline intravenously in a 3-ml volume. All measure-

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Address correspondence to Dr. Bailey, Department of Anesthesiology, University of Utah School of Medicine, 3C-444, 50 North Medical Drive, Salt Lake City, UT 84132.

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ments were repeated 5 min after reversal (60 min after the morphine had been injected), as well as 90, 120, 180, and 240 min after the morphine. Subjects received intravenous injections of the other two test solutions at two additional (separate) sessions. The subjects and investigators were blinded as to drug identity at all sessions. The sequence of drugs for the three sessions was a completely balanced design with two replications of each permutation.

Rebreathing Circuit and Measurement

A modified Read rebreathing circuit was used in this study. The rebreathing apparatus includes a 7.5-L Neoprene rebreathing bag enclosed in a lucite box. A Validyne differential pressure transducer measuring the pressure drop across a Fleisch pneumotachograph at the outlet of the box allowed determination of ventilatory flow. Flow was directed either into the bag or through the pneumotachograph by a three-way valve located at the mouth of the box, permitting the subject to breathe room air when not rebreathing CO_2. Inspiratory and expiratory limbs of the circuit were separated by a Collins J-Valve. A solenoid operated occlusion valve was located near the mouthpiece end of the inspiratory airway. CO_2 concentration was measured by a Beckman LB-2 Infrared CO_2 Analyzer that sampled gas at the mouthpiece at a rate of 200 ml/min and returned it to the central chamber of the Collins valve. Airway occlusion pressure was measured by a Microswitch pressure transducer in the central chamber of the Collins valve. The pressure signal was low pass filtered at 30 Hz. Total circuit volume was 9 L. Inspiratory circuit resistance was 1.9 cm $H_2O{\cdot}L^{-1}{\cdot}sec^{-1}$, and expiratory circuit resistance was 1.7 cm $H_2O{\cdot}L^{-1}{\cdot}sec^{-1}$. Resistances were constant between flow rates of 15 and 135 L/min.

Flow, CO_2, and pressure signals were sampled by a microcomputer (Motorola Exorciser 2) from a 12-bit analog to digital (A/D) convertor (Burr–Brown MP7208 Data Acquisition System) with resolution of 4.8 mV per A/D unit and range of ± 10 volts. Occlusion pressure ($P_{0.1}$) measurements were made at the start of every inspiration. The inspiratory occlusion valve was closed 300 msec after the start of expiration. If the shape of the occluded pressure waveform was satisfactory, inspiration pressure was sampled and stored ($P_{0.1}$). A signal to reopen the valve was sent 120 msec after the onset of inspiration.

Rebreathing Data Collection and Analysis

After allowing the subject to breathe quietly through the mouthpiece with a noseclip in place, resting $P_{ET_{CO_2}}$ was recorded, and the three-way valve was switched to the rebreathing bag previously filled with 7.8% CO_2 and 92.2% O_2. At this time the subject took three deep breaths and then resumed normal breathing. For each breath, the following data were displayed on a video terminal and stored in memory: inspiratory time (T_i), breath duration (T_{tot}), fractional inspired and end-tidal CO_2 concentration (% $INCO_2$; % $ETCO_2$), tidal volume (V_T), minute ventilation ($\dot{V}_E$), inspiratory mouth occlusion pressure at 100 msec ($P_{0.1}$), and elapsed time since start of CO_2 rebreathing. All gas volumes were corrected to BTPS. Subjects were encouraged to rebreathe as long as possible, but could stop at any time; the desired goal was to reach a $P_{ET_{CO_2}}$ of 65 mm Hg. The change in $P_{ET_{CO_2}}$ during rebreathing challenges was always an increase of at least 15 mm Hg.

After completion of each CO_2 challenge, plots of minute ventilation ($\dot{V}_E$) vs $P_{ET_{CO_2}}$, and $P_{0.1}$ vs $P_{ET_{CO_2}}$ were displayed on the video display terminal. To ensure that the regression line reflected only data from the linear portion of the ventilatory response, data from the first five breaths were excluded from analysis. Data from all other breaths were used for least squares linear regression. Resting $P_{ET_{CO_2}}$, the slope of $\dot{V}_E$ vs $P_{ET_{CO_2}}$, and the slope of $P_{0.1}$ vs $P_{ET_{CO_2}}$ were saved for analysis at a later time.

Pain Threshold Measurement

Pain threshold was determined using a Grass S88 stimulator and stimulation isolation unit (Grass medical instruments) and a constant current unit (Grass medical instruments CCU IA) to deliver an electrical stimulus (square wave, 60 Hz) of 0.4 sec in duration through a concentric (Tursky) electrode (Farral Instruments) applied to the dorsal nondominant forearm (8,9,10).

The electrode was applied to the skin after shaving the area and preparing it with an abrasive cream. After removing the abrasive cream, electrode contact was insured with a standard conductive gel. Initial current applied was below sensation threshold, the current then being increased by 0.2 to 0.5 mamps every 5 sec until the subject described the current as painful (pain threshold). Three such measurements were taken and averaged at each test time.

Statistical Analysis

The effect of morphine and a comparison of the effects of placebo, nalbuphine, and naloxone on respiratory variables (resting $P_{ET_{CO_2}}$, slope $\dot{V}_E/P_{ET_{CO_2}}$, slope $P_{0.1}/P_{ET_{CO_2}}$) and pain threshold was performed by paired *t*-test, analysis of variance (ANOVA), repeated

Table 1. Resting PET$_{CO_2}$ (mm Hg) before and after 0.21 mg/kg Intravenous Morphine Sulfate

Injection given 55 min after morphine	Baseline	Minutes after morphine 5	30	60 (5)[a]	120 (65)	240 (185)
Saline	40.3 ± 0.7	44.0 ± 1.0	45.3 ± 0.9	45.2 ± 1.0	45.8 ± 1.0	46.0 ± 0.9
Naloxone	40.6 ± 1.1	44.6 ± 1.1	45.8 ± 1.0	42.9 ± 1.4[b]	44.2 ± 1.1	44.8 ± 1.3
Nalbuphine	40.0 ± 0.9	43.8 ± 1.3	44.3 ± 0.9	46.5 ± 0.9[c]	46.3 ± 0.9	45.6 ± 1.2

[a] Numbers in parentheses indicate minutes after postmorphine injection.
[b] $P = 0.005$, naloxone effect 5 min after injection (60 min after morphine) compared to 30 min after morphine.
[c] $P = 0.038$, nalbuphine effect 5 min after injection (60 min after morphine) compared to 30 min after morphine.

measures ANOVA, repeated measures analysis of covariance (ANCOVA), and nonparametric Wilcoxon signed ranks test. The P1D, P3D, P3S, and P2V programs within the BMDP statistical package were used for statistical computations. (BMDP Statistical Software, Department of Biomathematics, UCLA. Berkeley, CA: University of California Press, 1981.) P values < 0.05 were considered statistically significant.

Results

The sample consisted of 12 subjects (5 females, 7 males) aged 21–36 yr (mean 28.75 yr). Mean weight was 71.5 kg (range 49–84 kg). All subjects had 15 or more years of education. Eight subjects were in medically related occupations.

Respiratory Effects: Resting PET$_{CO_2}$ (Table 1)

Mean baseline values for the resting PET$_{CO_2}$ of the 12 subjects at the three different testing sessions ranged from 40.0 to 40.6 mm Hg; there was no significant difference among these values. Morphine alone produced statistically significant increases in the resting PET$_{CO_2}$ at 5 and 30 min after injection. There was no difference in the degree of morphine-induced respiratory depression at the three testing sessions.

Comparing the resting PET$_{CO_2}$ 30 min after morphine and 5 min after naloxone, nalbuphine, or saline, we found a significant difference in the way the three injections affected resting PET$_{CO_2}$. There was no change in PET$_{CO_2}$ with saline, a significant decrease in PET$_{CO_2}$ after naloxone, and a further, statistically significant increase in PET$_{CO_2}$ after nalbuphine.

Comparing resting PET$_{CO_2}$ levels at 30 min and 4 hr after morphine, we found there was no longer a significant difference among the three postmorphine injections. This is consistent with renarcotization after naloxone administration. The increased respiratory depression after nalbuphine also dissipated. Figure 1 schematically presents the changes in the resting PET$_{CO_2}$ over time in all three groups.

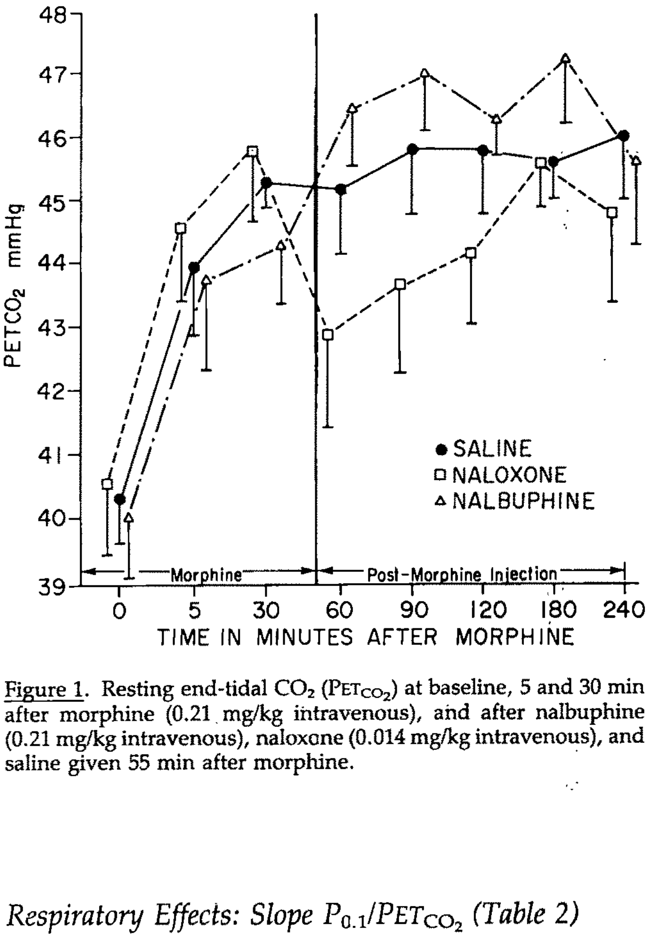

Figure 1. Resting end-tidal CO$_2$ (PET$_{CO_2}$) at baseline, 5 and 30 min after morphine (0.21 mg/kg intravenous), and after nalbuphine (0.21 mg/kg intravenous), naloxone (0.014 mg/kg intravenous), and saline given 55 min after morphine.

Respiratory Effects: Slope P$_{0.1}$/PET$_{CO_2}$ (Table 2)

Mean baseline values for the P$_{0.1}$/PET$_{CO_2}$ slopes of the 12 subjects at the three different testing sessions ranged from 0.42 to 0.48 cm H$_2$O/mm Hg; there was no significant difference between these values. Morphine alone produced significant decreases in slope P$_{0.1}$/PET$_{CO_2}$ at 5 and 30 min. There was no difference in the degree of morphine-induced respiratory depression at the three testing sessions.

Comparing the slopes at 30 min after morphine and 5 min after reversal (60 min after morphine), we found a significant difference in the response of the P$_{0.1}$/PET$_{CO_2}$ slope 5 min after the three reversal drugs. There was no change with saline, significant reversal

Table 2. The Slope of the Occlusion Pressure Response to CO_2 ($P_{0.1}/PET_{CO_2}$) in cm H_2O/mm Hg before and after 0.21 mg/kg Intravenous Morphine

Injection given 55 min after morphine	Baseline	Minutes after morphine 5	30	60 (5)[a]	120 (65)	240 (185)
Saline	0.42 ± 0.07	0.22 ± 0.03	0.21 ± 0.04	0.23 ± 0.2	0.35 ± 0.1	0.26 ± 0.05
Naloxone	0.44 ± 0.06	0.24 ± 0.06	0.23 ± 0.04	0.45 ± 0.08[b]	0.32 ± 0.05	0.32 ± 0.07
Nalbuphine	0.48 ± 0.1	0.18 ± 0.02	0.20 ± 0.03	0.17 ± 0.03	0.18 ± 0.03	0.22 ± 0.05

[a] Numbers in parentheses indicate minutes after postmorphine injection.
[b] $P = 0.005$, naloxone effect 5 min after injection (60 min after morphine) compared to 30 min after morphine.

of depression with naloxone, and no significant change with nalbuphine.

Comparing $P_{0.1}/PET_{CO_2}$ slopes at 30 min and 4 hr after morphine, we found there was no longer a difference among the three postmorphine injections. This is consistent with renarcotization after naloxone administration. Figure 2 schematically presents the changes in the $P_{0.1}/PET_{CO_2}$ slope over time in all three groups.

Respiratory Effects: Slope $\dot{V}E/PET_{CO_2}$ (Table 3)

Mean baseline values for the $\dot{V}E/PET_{CO_2}$ slopes of the 12 subjects at the three different testing sessions ranged from 1.52 to 1.67 $L\cdot min^{-1}\cdot mm^{-1}$ Hg; there was no difference among these values. Morphine alone produced significant decreases in the $\dot{V}E/PET_{CO_2}$ slope at 5 and 30 min. There was no significant difference in the degree of morphine-induced respiratory depression at the three testing sessions.

Comparing the slopes 30 min after morphine and 5 min after reversal (60 min after morphine), we found a significant difference in the $\dot{V}E/PET_{CO_2}$ slope 5 min after the three postmorphine injections. There was no change with saline, significant reversal of depression with naloxone, and no change with nalbuphine.

Four hours after morphine there was no difference among the three groups. There was no renarcotization evident 3 hr after naloxone administration.

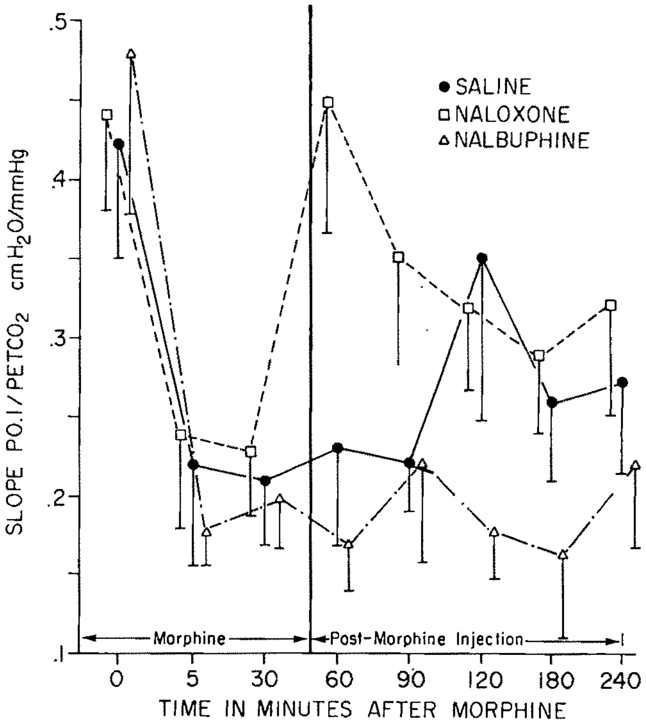

Figure 2. Slope of the occlusion pressure response to CO_2 rebreathing ($P_{0.1}/PET_{CO_2}$) at baseline, 5 and 30 min after morphine (0.21 mg/kg intravenous), and after nalbuphine (0.21 mg/kg intravenous), naloxone (0.014 mg/kg intravenous), and saline given 55 min after morphine.

Pain Threshold (Table 4)

Mean control values for the pain threshold of the twelve subjects at the three different testing sessions ranged from 4.6 to 5.6 mamps; there was no significant difference between these values. Morphine alone significantly increased pain threshold at 5 and 30 min. The increase in pain threshold was significantly greater at 30 than at 5 min after morphine. There was no significant difference in the degree of morphine-induced analgesia at the three testing sessions.

Comparing pain thresholds 30 min after morphine and 5 min after saline, naloxone, or nalbuphine, we found a statistically significant difference in the way the postmorphine injections affected the pain threshold. Naloxone significantly lowered the pain threshold, whereas neither nalbuphine nor saline significantly altered the pain threshold. Four hours after morphine there was no significant difference among the three postmorphine injection drugs.

Discussion

The results of this study indicate that nalbuphine does not always antagonize opioid induced respiratory depression. Specifically, we found that 0.21 mg/kg of intravenous nalbuphine given 55 min after 0.21 mg/kg

Table 3. The Slope of the Ventilatory Response to CO_2 ($\dot{V}\text{E}/\text{PET}_{CO_2}$) before and after 0.21 mg/kg Intravenous Morphine

Injection given 55 min after morphine	Baseline	Minutes after morphine 5	30	60 (5)[a]	120 (65)	240 (185)
Saline	1.67 ± 0.25	1.03 ± 0.17	1.00 ± 0.19	1.10 ± 0.19	1.46 ± 0.25	1.42 ± 0.20
Naloxone	1.54 ± 0.25	1.15 ± 0.21	1.27 ± 0.24	1.53 ± 0.22[b]	1.52 ± 0.30	1.48 ± 0.27
Nalbuphine	1.60 ± 0.22	0.85 ± 0.18	0.92 ± 0.20	1.08 ± 0.17	1.28 ± 0.17	1.30 ± 0.25

[a] Numbers in parentheses indicate minutes after postmorphine injection.

[b] $P = 0.001$, naloxone effect 5 min after injection (60 min after morphine) compared to 30 min after morphine.

Table 4. Current (mamp) Judged Painful (Pain Threshold) before and after 0.21 mg/kg Intravenous Morphine

Injection given 55 min after morphine	Baseline	Minutes after morphine 5	30	60 (5)[a]	120 (65)	240 (185)
Saline	4.6 ± 0.7	6.0 ± 1.0	6.3 ± 1.0	6.2 ± 1.0	6.2 ± 1.1	5.6 ± 1.0
Naloxone	5.6 ± 1.1	6.6 ± 1.3	7.6 ± 1.4	6.3 ± 1.3[b]	6.4 ± 1.4	6.2 ± 1.3
Nalbuphine	4.8 ± 0.7	5.9 ± 1.1	6.2 ± 1.1	6.0 ± 1.0	6.1 ± 1.1	5.8 ± 1.1

[a] Numbers in parentheses indicate minutes after postmorphine injection.

[b] $P < 0.05$ compared to 30 min after morphine (see text for explanation).

of intravenous morphine sulfate further depressed ventilation in healthy adult volunteers. On the other hand, 0.014 mg/kg of intravenous naloxone temporarily reversed the respiratory depression produced by 0.21 mg/kg of morphine sulfate.

Several clinical reports indicate that nalbuphine has been successfully used as an opioid antagonist after anesthesia (4–7). The doses of narcotic analgesic/anesthetic used in these studies varied but were usually large. Latasch et al. (6) administered 22.7 ± 6.0 μg/kg of fentanyl for operations lasting 80 ± 36 min in general surgical patients and concluded that 20 mg of intravenous nalbuphine, given as a single dose, promptly and totally antagonized fentanyl-induced apnea. Tabatabai et al. (5) reported that 0.1 mg/kg of intravenous nalbuphine reversed respiratory depression in male patients who received 28.5 ± 2 ml of fentanyl for unspecified operations lasting 5.4 ± 0.3 hr. Moldenhauer et al. (7) found nalbuphine (administered in 15-μg/kg increments) antagonized respiratory depression when given several hours or more after anesthesia with up to 120 ± 7 μg/kg of fentanyl for aortocoronary bypass surgery, but noted some difficulties with hypertension as well as renarcotization. In light of our findings, and the fact that nalbuphine itself is a respiratory depressant (1,2), it is apparent that the effect of nalbuphine is dependent upon whether or not other opioids are previously administered and in what amount.

Opioid-induced respiratory depression is considered to be primarily related to agonist activity at the μ receptor. Studies by Romagnoli and Keats (2) and Gal et al. (1) indicate that the maximum respiratory depressant effects of nalbuphine are similar to those produced by about 30 mg/70 kg of morphine in healthy young adults. This may explain why we found no reversal effect with the doses of morphine and nalbuphine used in this study. It is possible that nalbuphine will antagonize opioid effects only after an opioid agonist dose greater than the equivalent of about 30 mg/70 kg of morphine. Perhaps after this dose, the weak or partial μ agonist nalbuphine displaces the more potent μ agonist and results in an apparent decrease in respiratory depression.

On the other hand, if nalbuphine is a pure antagonist at the μ receptor and an agonist at the κ receptor (where its mild respiratory depression is possibly produced) (11), it is possible that a smaller dose of nalbuphine, e.g., 2–4 mg, could produce different results. In this case, antagonism at the μ receptor may require less nalbuphine than agonism at the κ receptor, due to differences in receptor affinity, and a smaller dose of nalbuphine than that used in our study could theoretically be a more effective opioid antagonist (12).

Various degrees of residual respiratory depression (e.g., Pa_{CO_2} values ranging from 36 to 50 mm Hg) have been reported after reversal of an opioid agonist by nalbuphine (3–7). Renarcotization necessitating close monitoring and redosage with nalbuphine has also been documented (7). The amount of opioid agonist administered and the time course of its elimination and termination of clinical effect obviously play important roles. The amount of surgical pain present also will probably influence respiratory drive after reversal with nalbuphine. Thus nalbuphine may not be optimal antagonist therapy in patients who have little postsurgical pain and/or may be placed at added risk with even moderately elevated Pa_{CO_2} (e.g., increased intracranial pressure). It is also not known whether nalbuphine will restore adequate respiration in patients (e.g., the elderly) who sometimes have profound respiratory depression from even small to moderate doses of opioids.

In this study the changes in pain threshold indicate that the analgesic effects of naloxone and nalbuphine paralleled the respiratory effects. Naloxone decreased pain threshold (antagonized morphine), whereas nalbuphine did not affect it. Others have reported findings suggesting that analgesia from nalbuphine coincides with its respiratory effect and that a ceiling exists for both (1). Although analgesia may be preserved when reversing respiratory depression with nalbuphine, the immediate onset or increase in pain has been reported with this practice (7). Additional doses of nalbuphine reportedly can alleviate such pain, perhaps through κ receptor-mediated analgesia, but the success rate of this approach is not known. Again, the type of operation and amount of postoperative pain is likely to significantly influence the results of opioid agonist reversal with nalbuphine.

The lack of uniform renarcotization with naloxone or a consistent increased effect after nalbuphine with all tests performed is most likely due to different degrees of variability within each test. Although the resting PET_{CO_2} clearly documents statistically significant renarcotization with naloxone as well as potentiation of respiratory depression with nalbuphine, the occlusion pressure and ventilatory response to CO_2 do not. We have previously found similar differences among these various tests (13). Our analgesic testing was also limited by a fairly large degree of variability as demonstrated by the standard error of the mean (Table 4).

Another problem we were confronted with was the method and dose of naloxone and nalbuphine to administer. Due to practical constraints in terms of study design and drug effect and duration, we chose to administer one large antagonist dose, realizing that this is not the optimal way to clinically administer opioid antagonists. Attempting to define equipotent doses for naloxone and nalbuphine was also difficult due to the different nature of the drugs. Based on our clinical experience and pilot studies, we chose doses we felt would maximize antagonism without exceeding the clinical dosage range. The inclusion of larger doses of morphine, e.g., 30 mg/70 kg and 45 mg/70 kg, would have perhaps permitted a better understanding of opioid antagonism with nalbuphine. Unfortunately, even if our foresight had equaled our hindsight, the practical constraints in performing such a study would have been considerable.

Despite these limitations, we believe that several clinical implications concerning the use of nalbuphine as an opioid antagonist can be made. First, where mild to moderate doses of an opioid have produced respiratory depression requiring antagonism, nalbuphine may not be reliable. Also, where even mild to moderate degrees of CO_2 retention are undesirable or contraindicated, nalbuphine should be avoided. Finally, the ability of nalbuphine to adequately antagonize severe respiratory depression that sometimes occurs from analgesic doses of opioid agonists is not known, and perhaps naloxone should be chosen as more reliable in these circumstances.

In summary, in young healthy volunteers 15 mg/70 kg of nalbuphine enhanced the respiratory depression produced by 15 mg/70 kg of morphine while naloxone, 1.0 mg/70 kg, temporarily antagonized respiratory depression induced by the same dose of morphine. Also, in these doses, naloxone antagonized morphine-induced analgesia, whereas nalbuphine did not. We conclude that small to moderate amounts of opioid agonist may not be reversed, and indeed may be potentiated by nalbuphine.

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Augmentation of Venous Return by Adrenergic Agonists during Spinal Anesthesia

John F. Butterworth IV, MD, William Piccione Jr, MD, Luis D. Berrizbeitia, MD, Garland Dance, BA, Richard J. Shemin, MD, and Lawrence H. Cohn, MD

BUTTERWORTH JF IV, PICCIONE W Jr, BERRIZBEITIA LD, DANCE G, SHEMIN RJ, COHN LH. Augmentation of venous return by adrenergic agonists during spinal anesthesia. Anesth Analg 1986;65:612–6.

To test the effectiveness of adrenergic agonists in correcting the vascular sequelae of spinal anesthesia, we used venous reservoir volume (RV) and mean arterial pressure (MAP) as indices of the changes in venous capacitance and arterial resistance produced by adrenergic agonists in dogs anesthetized with pentobarbital and undergoing cardiopulmonary bypass (CPB). A CPB-based technique was chosen both to prevent drug and reflex effects on the heart from influencing the results and to provide a convenient means by which to monitor venous capacitance. Total spinal anesthesia significantly decreased both RV and MAP relative to steady-state CPB values. Return of these hemodynamic alterations to baseline was attempted using pure α- and β-adrenergic agonists, and a mixed adrenergic agonist (phenyl-ephrine, isoproterenol, and ephedrine, respectively). Isoproterenol increased RV, but further decreased MAP. Phenyl-ephrine increased MAP but not RV. Ephedrine increased both MAP and RV. We conclude that a mixed adrenergic agonist such as ephedrine more ideally corrects the noncardiac circulatory sequelae of spinal anesthesia than does either a pure α- or β-adrenergic agonist.

Key Words: ANESTHETIC TECHNIQUES, SPINAL. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—vasopressors.

Spinal anesthesia has profound effects on cardiovascular function, particularly when autonomic blockade includes thoracic dermatomes. These effects result primarily from loss of sympathetic tone in resistance and capacitance vessels, which leads to decreased MAP and to relative hypovolemia (1). The means to quantify these hemodynamic changes remain controversial. To define the circulatory effects of spinal anesthesia, previous studies have measured changes in central venous pressure, pulmonary arterial pressure, and MAP, or changes in limb vessel flow or volume (2,3). Unfortunately, unless cardiac output remains constant, a secondary change in heart rate or contractility may obscure the true extent of change in any of these variables.

The choice of pharmacologic agent to reverse these cardiovascular effects of spinal anesthesia is also an unsettled issue. Investigators have compared drug effects on isolated arteries and veins, without recognizing that central venous volume changes might not be well-modeled by cutaneous vessels (4). Other researchers have measured the effects of catecholamines on venous capacitance and arteriolar resistance during cardiopulmonary bypass (CPB) with a fixed cardiac output, but have failed to block autonomic reflexes (e.g., with spinal anesthesia) as part of their experimental preparation (5–13). Cardiopulmonary bypass techniques are especially useful because during constant pump flow arterial pressure reflects arterial resistance and venous reservoir volume (RV) reflects venous capacitance.

The purpose of this study was to determine the effects of total spinal anesthesia on MAP and RV, and to compare the ability of phenylephrine (an α-agonist), isoproterenol (a β-agonist), and ephedrine (a mixed α- and β-agonist) to return RV and MAP to control levels during conditions of constant pump flow.

Methods

Twenty adult greyhounds, mean weight 25 ± 2 kg (SD), were anesthetized with intravenous thiopental

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Address correspondence to Dr. Butterworth, Department of Anesthesia, Bowman Gray School of Medicine, 300 South Hawthorne Rd., Winston-Salem, NC 27103.

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(25 mg/kg) and pentobarbital (5 mg/kg). The dogs then underwent tracheal intubation and mechanical ventilation with 100% oxygen. Anesthesia was maintained with intravenous pentobarbital (1 mg/kg) at hourly intervals. Arterial and central venous catheters were placed in femoral vessels. A 19 gauge epidural catheter was inserted through a 17 gauge Weiss epidural needle into the cisterna magna, and correct placement was confirmed by free flow of cerebrospinal fluid through the catheter. The CPB circuit was primed with 2 L of lactated Ringer's solution. The spleen was excised to eliminate changes in RV attendant to catecholamine-induced contraction of its muscular capsule (14). Median sternotomy was performed. Heparin (4 mg/kg) was injected into the right atrium.

Normothermic CPB was initiated via right atrial and femoral cannulae at a flow of 75 $ml\cdot kg^{-1}\cdot min^{-1}$ using a Sarns (Ann Arbor, MI) Model 1800 bypass pump and Shiley (Irvine, CA) Model S100A oxygenators. The heart was fibrillated with topical ice to establish total CPB. Venous return drained by gravity into a calibrated reservoir approximately 30 cm below the level of the right atrium. Arterial pH, and oxygen and carbon dioxide tensions were maintained within normal ranges (7.40 ± 0.05, >100 mm Hg, and 40 ± 5 mm Hg, respectively) and kept constant during drug testing by altering CPB pump gas flows or by administering intravenous bicarbonate in the rare instances when this was necessary.

After the steady-state MAP (mean 49 ± 12 mm Hg (SD)) and RV (1–1.5 L, depending on the rate of insensible fluid loss during CPB) were recorded, total spinal anesthesia was induced by the injection of 20 mg of hyperbaric tetracaine through the cisternal catheter, our pilot studies in awake dogs having indicated that this dose of tetracaine reliably produces all effects of total spinal anesthesia, including insensibility and apnea. At this stage, four dogs were eliminated from the study, two because of excessive bleeding and two because of unexplained metabolic acidosis.

In seven of the remaining dogs, mean weight 25 ± 1 kg (SD), correction of the resulting hemodynamic changes was attempted by the use of phenylephrine (an α-agonist), isoproterenol (a β-agonist), or ephedrine (a mixed α- and β-agonist). Each animal served as its own control. The drugs were administered randomly according to the following protocol: phenylephrine and isoproterenol were given by constant intravenous infusions in increasing doses; ephedrine was given by bolus intravenous injections. Because of its prolonged duration of action, no additional drugs were given after ephedrine. Because of this constraint, and in order to limit bypass time to 120 min, not all animals received all doses of each drug. Infusions were continued and data were recorded for a full 3 min at each dose to ensure that a steady-state had been reached, a pilot study having shown no additional advantage to recording data or continuing infusions for 5- or 10-min periods. Each animal received all that was to be given of one drug before another drug was given. Again, because of limitations of time, hemodynamic variables were not allowed to return to baseline between doses of a drug. Then, before the next drug was given, the animal was rested for an interval comparable to the total infusion time for the preceding drug so that a steady-state would be present at the start of the next series of doses.

All animals received 1 L of lactated Ringer's solution before sternotomy, and a constant infusion of crystalloid (20 $ml\cdot kg^{-1}\cdot hr^{-1}$) before CPB. During CPB, fluid was given to each dog in boluses between drug tests as necessary (typically a total of 1–1.5 L was given). These boluses produced the expected changes in RV (e.g., 0.5 L immediately raised RV by roughly 0.5 L). Venous reservoir volume changes were corrected to account for constant insensible fluid loss sustained throughout each experiment. We defined this loss as the difference, if any, between the RV measured after the final dose of the final drug had dissipated and that recorded immediately before the first dose of the first drug was infused. Fluid given during CPB was added to this total. Statistical comparison with control values was assessed by analysis of variance (ANOVA) and paired *t*-test.

The remaining nine animals were used in studies testing other drugs, and those results will be reported separately.

Results

Total spinal anesthesia in the 16 dogs caused pooling of venous blood and loss of arteriolar tone reflected at steady-state as decreased RV (−5.6 ± 3.3 ml/kg (mean ± SD) $n = 15$, $P < 0.001$) and decreased MAP (−30.7 ± 18.8%, $n = 16$, $P < 0.001$) when compared to steady-state, prespinal anesthesia values. In the seven study dogs, each drug dose when administered during total spinal anesthesia at steady-state produced its maximal effect within 90 sec, then maintained those hemodynamic effects throughout the observation period for that drug. These results are displayed in Table 1. Isoproterenol increased RV in a reversible, dose-dependent manner, but lowered MAP compared with steady-state postspinal anesthesia measurements. Phenylephrine increased MAP in a dose-dependent, reversible manner, but had no clear effect on RV. These dose-dependent effects of phenylephrine and

Table 1. Circulatory Response to Adrenergic Agonists during Total Spinal Anesthesia in Seven Dogs

Drug dosage	Total cumulative dose by end of measurement (μg/kg)	Change in MAP (%)	Change in RV (ml/kg)	Number of observations
Phenylephrine[a] ($\mu g \cdot kg^{-1} \cdot min^{-1}$)		(Baseline MAP = 44 ± 8 mm Hg)		
0.05	0.15 ± 0	2.0 ± 9.8	0.1 ± 1.8	4
0.50	1.60 ± .07	1.8 ± 8.5	0.2 ± 1.8	6
5.00	16.60 ± .07	24.4 ± 21.9	0.3 ± 3.3	6
10.00	46.62 ± .07	74.4 ± 37.2[b]	−1.6 ± 6.4	5
20.00	106.61 ± .06	160.0 ± 31.8[b]	−6.6 ± 7.0	4
Isoproterenol[a] ($\mu g \cdot kg^{-1} \cdot min^{-1}$)		(Baseline MAP = 50 ± 7 mm Hg)		
0.005	0.015 ± 0	−2.7 ± 4.6	−1.4 ± 2.3	3
0.050	0.161 ± .006	−23.4 ± 19.3	1.1 ± 3.4	4
0.500	1.661 ± .006	−37.7 ± 18.6	4.5 ± 4.3	4
1.000	4.665 ± 0	−38.7 ± 14.7[b]	7.7 ± 4.1[b]	3
Ephedrine[c] (μg/kg)		(Baseline MAP = 35 ± 4 mm Hg)		
200	200 ± 0	33.0 ± 16.5[b]	5.1 ± 2.9[b]	4
1000	1200 ± 0	91.0 ± 28.0[b]	9.7 ± 1.2[b]	4

Values are mean ± SD.

Abbreviation: RV, volume in venous reservoir of cardiopulmonary bypass circuit.

[a] Each infusion continued for 3 min. Animals received doses of one drug in succession (without return of MAP to baseline) before any dose of another drug was given.

[b] $P < 0.05$

[c] Bolus injections given 3 min apart.

isoproterenol achieved statistical significance at higher doses. Ephedrine significantly increased both RV and MAP at both doses tested. These results also appear in Table 1.

Discussion

The marked decreases in MAP and RV observed after total spinal anesthesia were indicative of expected arteriolar dilatation and increased venous capacitance. Of the three adrenergic agonists we studied, only the mixed agonist, ephedrine, increased both MAP and RV.

The experimental design attempted to overcome the difficulties of measuring the circulatory effects of adrenergic agonists by modeling the systemic circulation during CPB as a simple three-compartment circuit (Fig. 1). In this model, arterial vessels constituted one compartment containing relatively small amounts of blood. The primary effect of this compartment on the systemic circulation was to regulate resistance to flow (and therefore the MAP). The venous compartment and the venous reservoir were modeled to contain the greatest part of the blood volume, but to have negligible effects on the resistance of the circuit. The blood in the venous vessels was considered to be in equilibrium with that in the rigid venous reservoir of the CPB circuit. Thus changes in the level of blood in the CPB reservoir resulted from changes in the capacitance of the venous system caused by, for example, catecholamine therapy or spinal anesthesia, or from changes in blood volume caused by, for example, transfusion or hemorrhage.

Although this approach certainly oversimplifies the systemic circulation during CPB, it does not have the limitations inherent in studying the effects of adrenergic agonists on single venous or arterial beds. Greene (1) has recommended agents combining both α- and β-effects (specifically mephentermine or ephedrine) for the treatment of spinal anesthesia-induced hypotension. He based his suggestion in part on a study by Zimmerman et al. (4), which showed relatively greater constriction of canine forelimb veins than arteries by these mixed agents than by pure α-agonists. However, Sutter's work (15) demonstrated the difficulty of predicting the systemic venous response to an adrenergic agonist based on observations of a single vein or venous bed. For example, he consistently found constriction, no effect, or dilatation, respectively, when venous strips from the rabbit external jugular veins, posterior vena cava, or anterior mesenteric veins were incubated with identical concentrations of isoproterenol. We believe that our steady-state measurements of RV in a CPB circuit provide a better index for alterations in total venous capacitance caused by spinal anesthesia or catecholamine therapy than do either size or flow characteristics of peripheral vessels.

Numerous investigators have used CPB techniques to study adrenergic pharmacology. Guyton et al. (16),

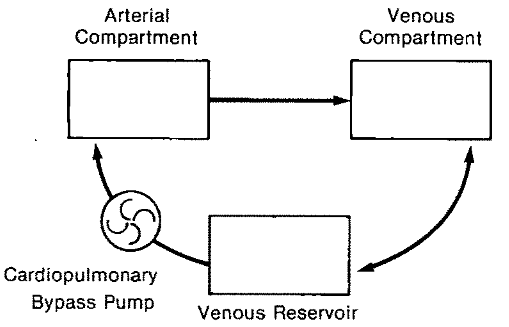

Figure 1. Three-compartment model for the circulation of blood during cardiopulmonary bypass.

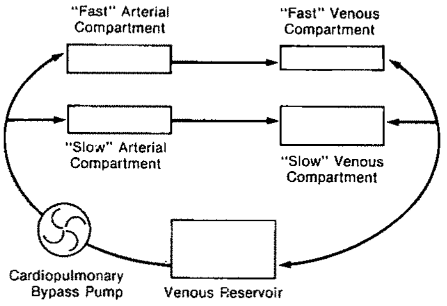
"Fast" Arterial Compartment
"Fast" Venous Compartment
"Slow" Arterial Compartment
"Slow" Venous Compartment
Cardiopulmonary Bypass Pump
Venous Reservoir

Figure 2. Modification of three-compartment model to account for blood flow differences between "rapid" and "slow" transit organs.

in their classic series of experiments that divided cardiac output into its systemic and myocardial components, used increasing doses of epinephrine to increase mean systemic pressure and thereby to augment venous return. Using metycaine, they produced total spinal anesthesia in all experiments to eliminate reflex circulatory changes. Using CPB but not spinal anesthesia, Green (5), Rutlen et al. (7), Emerson (8), Braunwald et al. (9), Kaiser et al. (10), Caldini et al. (11), and Müller-Ruchholtz et al. (13) measured flow and volume changes caused by β-adrenergic agonists that were consistent with a drug-induced increase in venous return. Imai et al. (6), also using general rather than spinal anesthesia, compared the ability of α-, β-, and mixed α-, β-agonists to produce changes in venous return. Both the mixed agonist norepinephrine and the β-agonist isoproterenol were found to increase the RV of a CPB circuit; the pure α-agonist methoxamine was ineffective. However, after treatment with propranolol (a β-blocker), neither norepinephrine nor isoproterenol increased RV. Imai et al. concluded that β-adrenergic agonists, but not α-adrenergic agonists, increased RV.

Measurements in all those studies except Guyton's could have been influenced by sympathoadrenal reflexes that would have been blocked by spinal anesthesia, and thus they did not address our clinical concerns regarding the hemodynamics of spinal anesthesia (6,10,12,13). Guyton did use spinal anesthesia, but did not study the drugs of greatest importance to the anesthetist. However, using the results of those studies, we could plan our study to provide two important additional pieces of information. First, we planned to examine critically the effects of spinal anesthesia on RV and MAP. Second, using a model that incorporated spinal anesthesia and a fixed cardiac output, we planned to compare the ability of α- and β-adrenergic agonists to influence RV.

We chose to produce total spinal anesthesia, rather than to limit blockade to midthoracic dermatomes, in order to ensure that the level of block would be uniform and easily maintained throughout each experiment. The usual disadvantages of total spinal anesthesia—block of medullary cardiac and respiratory centers and loss of consciousness—do not apply to anesthetized animals on total CPB. On the other hand, with constant pump flow and oxygenation, the effects of efferent autonomic blockade should be comparable to those produced when spinal anesthesia blocks are no higher than upper thoracic dermatomes.

We chose pentobarbital as our basal anesthetic to minimize the influence of the general anesthetic agent on our experimental results. Using pentobarbital anesthesia, we could not decrease overall venous capacitance (i.e., we could not increase RV) with even our highest dose of phenylephrine. Our data confirmed those of Imai et al. (6), as we had suspected they would. However, our findings contrast with those from a study by Müller-Ruchholtz et al. in which a morphine-based general anesthetic was used and in which there was an increase in RV after α-adrenergic treatment (12). Morphine has been identified as causing profound decreases in RV in both animal and human studies (17–19), and we suspect that its use as the basal anesthetic in the experiments by Müller-Ruchholtz et al. influenced their results.

The question of how the generally vasodilating agent isoproterenol could cause "venoconstriction" and increase venous return deserves comment. We speculate that β-adrenergic receptor stimulation increases venous return in much the same way that cross-clamping the aorta at the diaphragm does (20,21), i.e., by decreasing blood flow through the splanchnic vasculature. The model we used (Fig. 1) can be further subdivided to include rapid transit and slow transit systems in parallel as separate entities, each with its own arterial and venous compartments. Included in the rapid transit system is the circulation to heart, brain, and kidneys, whereas the main component of the slow transit system is the splanchnic vascular bed

(Fig. 2). If β-adrenergic receptor stimulation were to redirect flow from the splanchnic bed, the net effect would be indistinguishable from that of a transfusion or of generalized venoconstriction. Our system would measure this effect as an increase in the RV. The concept that redistribution of blood flow, rather than venoconstriction, is the mechanism by which β-adrenergic agonists increase venous return is supported by the work of Green (5), Rutlen et al. (22), and Permutt and Caldini (21).

Regardless of mechanism, our findings are consistent with those of most other investigators and support the conclusion that a mixed adrenergic agonist, such as ephedrine, provides more appropriate drug treatment for the noncardiac circulatory sequelae of spinal anesthesia than either a pure α- or a pure β-adrenergic agonist.

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ANESTH ANALG
1986;65:617–24

Roles of Fentanyl and Nitroglycerin in Prevention of Myocardial Ischemia Associated with Laryngoscopy and Tracheal Intubation in Patients Undergoing Operations of Short Duration

J. Fusciardi, MD, G. Godet, MD, J. M. Bernard, MD, M. Bertrand, MD, E. Kieffer, MD, and P. Viars, MD

FUSCIARDI J. GODET G, BERNARD JM, BERTRAND M, KIEFFER E, VIARS P. Roles of fentanyl and nitroglycerin in prevention of myocardial ischemia associated with laryngoscopy and tracheal intubation in patients undergoing operations of short duration. Anesth Analg 1986;65:617–24.

The purpose of this study was to evaluate intravenous nitroglycerin given during induction of anesthesia as a means for prevention of myocardial ischemia and hemodynamic changes associated with induction, laryngoscopy, and intubation, in patients with stable angina scheduled for vascular operations of moderate duration. Forty-six patients were randomly assigned to receive either fentanyl, 3 μg/kg (group 1, n = 6), fentanyl, 8 μg/kg (group 2, n = 20), or fentanyl 3 μg/kg plus a continuous intravenous nitroglycerin infusion, 0.9 μg·kg⁻¹·min⁻¹ (group 3, n = 20), in addition to thiopental–pancuronium anesthetic induction, prior to laryngoscopy and intubation. The criteria for recognizing myocardial ischemia were the following: horizontal or downsloping ST segment depression equal to or greater than 1 mV, and/or ventricular arrhythmia, on CM5 recording. In group 1, myocardial ischemia occurred during laryngoscopy and intubation in four patients, and mean blood pressure (MBP), heart rate, and mean pulmonary wedge pressure (PCWP) increased significantly (P < 0.05). Despite greater stability in MBP and heart rate in group 2, myocardial ischemia still occurred in four patients (not significantly different from group 1). Nitroglycerin added to low-dose fentanyl (group 3) produced significant reduction in myocardial ischemia (1/20) when compared with group 1 (P < 0.01), and significantly greater stability in PCWP during laryngoscopy and intubation in comparison to groups 1 and 2. In patients with stable angina undergoing operations of short duration, the use of nitroglycerin infusion and low-dose fentanyl significantly decreases the incidence of myocardial ischemia associated with induction of anesthesia and tracheal intubation.

Key Words: INDUCTION—anesthesia. HEART—ischemia. INTUBATION, TRACHEAL.

After induction of anesthesia with thiopental, circulatory responses to laryngoscopy and tracheal intubation often include tachycardia and increases in arterial (1) and pulmonary capillary wedge pressures (PCWP) (2). In patients with coronary artery disease, induction and tracheal intubation are the periods of anesthesia where the risk of myocardial ischemia is highest (3). High-dose fentanyl–oxygen anesthesia, widely recommended in such patients, effectively prevents hemodynamic and electrocardiographic changes during intubation (4). However, high-dose fentanyl results in prolonged loss of consciousness, and postoperative respiratory support is often required. For these reasons, high-dose fentanyl cannot be recommended in patients with coronary artery disease undergoing surgical procedures of short duration, or surgery requiring early postoperative evaluation of neurological status, as in patients undergoing carotid endarterectomy. In such situations low-dose fentanyl, 4–8 μg/kg, used as an adjunct to thiopental–pancuronium, might be of value, because postoperative recovery is more rapid, and hemodynamic response to laryngoscopy and intubation may be blunted both in hypertensive patients (2,5) and in patients at risk for the development of myocardial ischemia (6). However, it is not clear whether low-dose fentanyl anesthesia fully prevents myocardial ischemia associated with laryngoscopy and tracheal intubation in patients with angina pectoris. Another potentially useful method is the utilization of nitroglycerin, which is known to prevent not only stress-induced pressor responses when administered by the

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Address correspondence to Dr. Fusciardi, Département d'Anesthésie-Réanimation, Groupe Hospitalier Pitie-Salpêtriere, 83 boulevard de l'Hôpital, 75651 Paris Cedex 13, France.

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intranasal route (7), but also intraoperative myocardial ischemia both during cardiac (8) and noncardiac surgery (9) when administered by continuous intravenous infusion.

The present study was designed to evaluate the efficacy of low-dose fentanyl at two dose levels and continuous nitroglycerin infusion in prevention of myocardial ischemia and pressor responses during laryngoscopy and tracheal intubation in patients with stable angina scheduled for operations of short duration.

Methods

The study consisted of forty-six patients with a history of angina pectoris but no history of previous myocardial infarction within the preceding 6 months who were scheduled to undergo short duration vascular surgery. Informed consent and the approval of our committee on human studies were obtained. Selection of patients was not based upon age or cardiac medications used preoperatively. Only patients with left bundle branch block were excluded; they were excluded because ST segment depression made difficult the interpretation of changes in ST segments associated with myocardial ischemia. Cardiac medications were continued on the morning prior to operation.

Anesthetic Management

Premedication consisted of intramuscular morphine, 0.1 mg/kg, and scopolamine, 0.007 mg/kg, 1 hr before insertion of a 7F triple lumen Swan–Ganz catheter and a radial arterial cannula, with local infiltration with lidocaine, 1%. Patients were then randomly assigned to one of the three following groups. In group 1 anesthetic induction was with thiopental (5–7 mg/kg) adequate to produce loss of consciousness, after which pancuronium, 0.1 mg/kg, and fentanyl, 3 μg/kg, were administered. Laryngoscopy was performed 2 min after starting the fentanyl administration and 4 min after administration of pancuronium. In group 2 timings of drug administrations were identical, except that thiopental, 3 mg/kg, and fentanyl, 8 μg/kg, were given. In group 3 doses of thiopental and fentanyl were the same as in group 1, but patients in group 3 also received a continuous infusion of nitroglycerin dissolved in a propylene glycol solvent (Lenitral Besins-Iscovesco Co.) and administered by an electrical medical pump with a propylene syringe and polyethylene tubing. The nitroglycerin infusion was begun 20 min before anesthetic induction at a rate of 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ after preinfusion of 500 ml saline. The rate of nitroglycerin infusion was increased every 5 min at 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and the mean rate of nitroglycerin used before induction was 0.90 ± 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Infusion of saline was continued during the increasing rates of nitroglycerin infusion to limit to 20 mm Hg the decrease in mean blood pressure (MBP) and to avoid an increase in heart rate greater than 15 beats/min. Pulmonary wedge pressure was monitored during infusion. The nitroglycerin infusion was maintained throughout the anesthetic procedure. All patients breathed 100% oxygen for a 5-min period prior to anesthetic induction and thereafter throughout the entire study.

One of our team performed laryngoscopy and intubation in each patient. After intubation, patients received manually assisted ventilation for 5 min before institution of mechanically controlled ventilation.

Monitoring of ECG and Hemodynamics

Electrocardiogram lead CM5 was continuously monitored by one of our team responsible for the prompt recognition and appropriate treatment of ischemia. In addition, ECG lead CM5, as well as systemic arterial pulmonary and pulmonary capillary wedge pressures (PCWP) were simultaneously recorded on a calibrated FM magnetic tape recorder (Hewlett-Packard 3964A). Records were subsequently used for retrospective analysis of ST segments and pressure curves by an independent reviewer. An ischemic episode was defined as an ischemic-type horizontal or downsloping ST segment depression equal to or greater than 1 mV and lasting for at least 0.8 msec and for more than three beats. Premature ventricular contractions were also considered as evidence of myocardial ischemia.

Heart rate, mean systemic arterial blood pressure (MPB), PCWP, mean right atrial pressure, and cardiac output (based on two or three serial determinations using the thermodilution technique) were also measured. Elevations in PCWP equal to or higher than 18 mm Hg were considered an abnormality that required appropriate treatment. Cardiac index, stroke index, and systemic arterial resistances (SAR) were calculated using standard formulas.

Timings of Hemodynamic Measurements

Measurements in the three groups (Fig. 1) were made at five times: first, just before the beginning of the protocol (baseline); second, 1 min before laryngoscopy , i.e., at the end of anesthetic induction; third, during laryngoscopy and intubation; fourth, 5 min after laryngoscopy while the patients were manually ventilated; and fifth, at the fifth minute of controlled ventilation. In addition, another measurement was

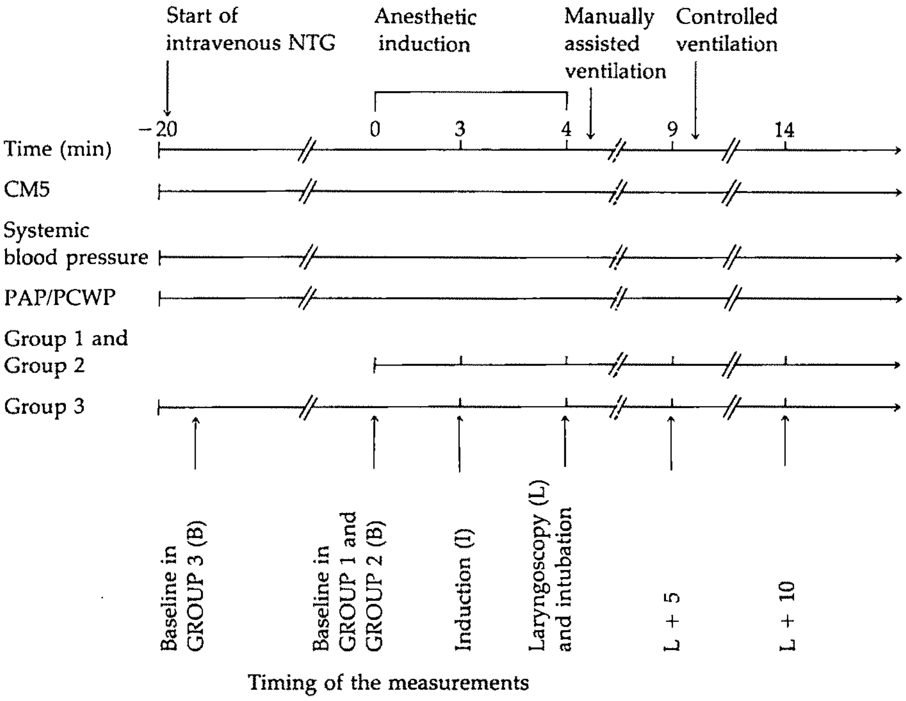

Figure 1. Representation of the protocol used in the three groups. Timing of nitroglycerin administration and anesthetic procedures is shown at the top of the figure. The successive times (indicated by arrows) when measurements were made are shown at the bottom of the figure. An additional point of measurement, not indicated on the figure, was taken in group 3 during nitroglycerin infusion at a mean dose of 0.9 $\mu g \cdot kg^{-1} \cdot min^{-1}$, just before starting the anesthesic induction, i.e., baseline in group 3 + 20 min.

taken in group 3 during infusion of nitroglycerin and saline, just before induction of anesthesia.

Statistical Analysis

The Kruskall and Wallis *H*-test was used to decide whether the three groups of patients belonged to an homogeneous population or to different populations. This test therefore was applied to initial clinical and hemodynamic status of the patients. Comparisons among groups were thereafter made using either the χ^2 test or Fisher's exact test (for comparison of the frequencies of ECG and PCWP abnormalities); Wilcoxon and Mann–Whitney tests were used to compare nonpaired hemodynamic values. Hemodynamic data in each group were analyzed using one-way analysis of variance and paired *t*-test. Statistical significance was assumed when $P < 0.05$.

Results

Clinical characteristics of the three groups are shown in Table 1. There were no statistically significant differences between groups in mean age, class of angina pectoris, incidence of hypertension, type of preoperative antianginal medications, or type and mean duration of surgical procedures. Volume of saline infused was greater in group 3 than in the other two groups. In the control group, no patient had a previous history of left ventricular failure (acute or subacute pulmonary edema).

Changes in the ST segment associated with myocardial ischemia occurred in three out of six of the control group during induction, laryngoscopy, or intubation (Table 2). Because of the high frequency of myocardial ischemia in the control group, it was decided to limit this group to the first six patients. Frequency of ST segment changes was not significantly less in group 2 (2/20) than in group 1. ST segment changes occurred mainly during and shortly after laryngoscopy and intubation (Table 2). No ST segment change was observed in group 3. The frequency of ST segment changes associated with myocardial ischemia was thus significantly reduced by the addition of nitroglycerin below the frequency of such changes in the control group ($P < 0.001$). In each case, after appropriate treatments such as additional injections of fentanyl and/or thiopental because of tachycardia or hypertension, and an intravenous bolus of nitroglycerin, 0.30 mg, in one case, no ischemic episode lasted more than 10 min.

Cardiac arrhythmias, i.e., ventricular premature contractions, were also observed (Table 2), but the frequency with which they occurred was not significantly different in the three groups. An abnormal elevation of A-C waves with an ECG ST segment change was observed during laryngoscopy in one patient in group 2 (Fig. 2).

In Table 2, ST segment changes, cardiac arrhythmias, and abnormalities in A-C and V waves are considered as evidence of myocardial ischemia. The number of patients who suffered myocardial ischemia was

Table 1. Clinical Characteristics in the Three Groups

Characteristic	Group 1 (fentanyl 3 μg/kg) $n = 6$	Group 2 (fentanyl, 8 μg/kg) $n = 20$	Group 3 (fentanyl, 3 μg/kg, with continuous nitroglycerin) $n = 20$
Age[a]	62 ± 16	64 ± 10	68 ± 8
Male/female ratio	6/0	15/5	17/3
Patients with previous myocardial infarction	1	3	2
Class of angina[b]			
2	2	9	7
3	2	8	7
4	2	3	6
Previous history of left ventricular failure	0[c]	7	5
Hypertension	3	15	13
Preoperative antianginal treatments			
β-Blocker	2	8	10
Calcium entry blocker	2	10	10
Nitrates	4	15	14
Volume of saline infusion (ml)[a]	433 ± 367	525 ± 290	1110 ± 398[d]
Type of surgery			
Carotid endarterectomy	5	16	16
Vertebral arterial surgery	1	2	2
Lumbar sympathectomy	0	1	1
Subclavian arterial surgery	0	1	1
Duration of operation (min)[a]	58 ± 15	54 ± 16	57 ± 18

[a] Values are mean ± SD.
[b] According to the New York Heart Association classification.
[d] $P < 0.01$, when compared to group 1 and group 2.
[c] $P < 0.05$, when compared to group 2 and group 3.

Table 2. Electrocardiographic and Hemodynamic Abnormalities Related to Myocardial Ischemia in the Three Groups

Patient numbers	ST segment depression	Ventricular premature contraction	Abnormality in A-C or V wave, suggesting acute dysfunction in ventricular compliance	Total frequency of events related to myocardial ischemia
Group 1				6/6
1	L	L + 5		
2	L			
3	L	I		
4		L + 10		
Group 2				8/20
1	I, L, L + 5			
2	L		A = 20 mm Hg (L)	
3		I, L + 10		
4		I		
Group 3				3/20
1		I, L, L + 5		

Abbreviations: L, laryngoscopy and intubation; I, Induction; L + 5, 5 min after laryngoscopy and intubation; L + 10, 10 min after laryngoscopy and intubation.

4 out of 6 in group 1, 4 out of 20 in group 2, and 1 out of 20 in group 3. The frequency of myocardial ischemia was thus not statistically less in group 2 than in group 1, but was significantly lower in group 3 than in group 1 ($P < 0.01$). There was no statistical difference in the incidence of myocardial ischemia between groups 2 and 3. Reporting these data in terms of total frequency of events related to myocardial ischemia, there were six such events in group 1, eight in group 2, and three in group 3. The incidence of events related to myocardial ischemia did not reach a statistically significant difference in groups 2 and 3 ($P = 0.07$).

Hemodynamic changes (Table 3) included significant increases above baseline levels in MBP (18%), heart rate (14%), PCWP (54%), and SAR (37%) as-

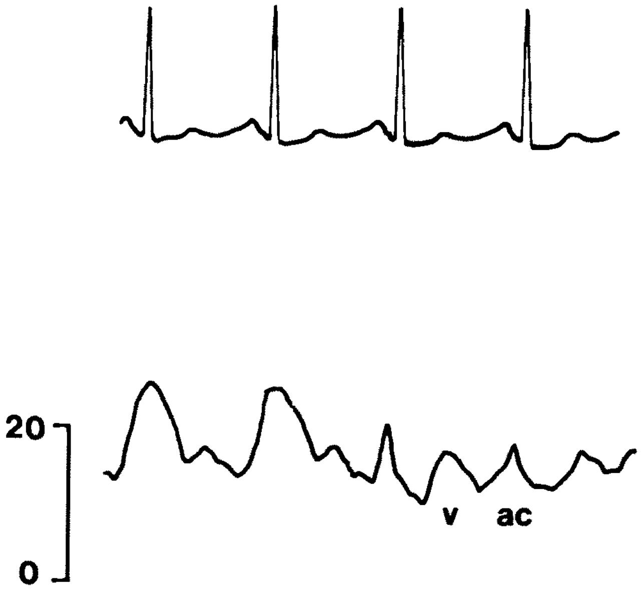

Figure 2. Myocardial ischemia associated with an abnormal rise in AC waves (18 mm Hg) occurring in one patient from group 2 five min after laryngoscopy. Acute left ventricular compliance dysfunction induced by ischemia is implied.

sociated with laryngoscopy and intubation in group 1. In group 2, laryngoscopy and intubation were associated with a 37% increase in SAR without significant changes above baseline values in MPB, heart rate, or PCWP. In group 3, infusion of nitroglycerin produced no significant change in MPB, heart rate, cardiac index, or PCWP prior to induction of anesthesia, but did result in a 19% reduction in SAR (Table 4). After anesthetic induction, a 19% decrease in MBP was observed in group 3, and laryngoscopy with intubation was associated with a 16% increase in heart rate (Table 3). In these three groups anesthetic induction was associated with comparable reductions in cardiac and stroke index.

Comparison of hemodynamic responses in groups 1 and 2 showed no statistically significant differences. On the other hand, MBP, PCWP, and SAR were significantly lower in group 3 than in group 1 during laryngoscopy and intubation ($P < 0.05$). Nitroglycerin decreased SAR before anesthetic induction, and so SAR was significantly more decreased in group 3 than in group 2 after anesthetic induction ($P < 0.05$) and remained lower in group 3 than in group 2 during laryngoscopy and intubation ($P < 0.05$). Because the reduction in cardiac index was comparable in the two groups (Table 3), MBP was significantly lower in group 3 than in group 2 after anesthetic induction ($P < 0.05$).

There were no statistically significant differences in mean values of PCWP during laryngoscopy and intubation in groups 3 and 2, but the frequency of sustained elevation in PCWP to or above 18 mm Hg was significantly more frequent in both groups 1 (4/6) and 2 (5/20) than in group 3 (0/20) ($P < 0.05$) (Fig. 3).

Discussion

Patients with ischemic heart disease often need surgical procedures for conditions unrelated to their coronary artery disease. Roy et al. (3) have shown that the incidence of ST segment depression in patients with coronary artery disease is greatest about the time of intubation as rate–pressure product increases. More recently Slogoff and Keat (10) emphasized the necessity for the prevention of myocardial ischemia by demonstrating a correlation between prebypass ischemia and postoperative infarction. However, only two methods have been shown to be effective in the prevention of myocardial ischemia and stress response induced by laryngoscopy and intubation in patients with coronary artery disease. Lunn et al. (4) have documented hemodynamic stability and prevention of myocardial ischemia with high-dose fentanyl (50 μg/kg) and oxygen anesthesia. However, this method can induce muscle rigidity and hypercapnia. Moreover, postoperative respiratory depression often leads to the need for prolonged mechanical ventilatory support. Thus for patients with coronary artery disease undergoing noncardiac surgical procedures, high-dose fentanyl anesthesia may not be a satisfactory means of preventing myocardial ischemia, especially when surgery is of short duration or when postoperative evaluation of neurologic status is needed, as after carotid endarterectomy. The second method for effective prevention of myocardial ischemia during induction of anesthesia, laryngoscopy, and intubation in patients with coronary artery disease, is based upon the use of nitroglycerin. For example intranasal administration of an nitroglycerin solution 1 min prior to the induction of anesthesia attenuates the pressor response to laryngoscopy and intubation of the trachea (7) is ASA I patients. In patients with coronary artery disease, intravenous nitroglycerin also prevents intraoperative myocardial ischemia during both cardiac (8) and noncardiac surgery (9). However, a dose of 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ would appear to be necessary, because no beneficial effect has been documented with a lower dose (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) (9,11).

Since 1982, when used as an adjunct to thiopental anesthesia in hypertensive patients, low or intermediate doses of fentanyl, ranging 5–8 μg/kg, have been said to reduce significantly both hormonal and hemodynamic response to laryngoscopy and intubation (2,6). Martin et al. have shown that this method can blunt

Table 3. Hemodynamic Responses

	Baseline	Induction	Laryngoscopy and intubation	L + 5 min	L + 10 min
Mean blood pressure (mm Hg)					
Group 1	106 ± 23	93 ± 15	124 ± 18[a,b]	99 ± 13	90 ± 7
Group 2	105 ± 18	96 ± 23	108 ± 29[b]	103 ± 25	90 ± 19
Group 3	93 ± 18	75 ± 14[a]	90 ± 21[b]	82 ± 25[a]	82 ± 20[a]
Heart rate (beats/min)					
Group 1	71 ± 17	79 ± 12[a]	81 ± 15[a]	77 ± 17	70 ± 16
Group 2	73 ± 17	74 ± 17	74 ± 20	74 ± 17	68 ± 15
Group 3	67 ± 12	74 ± 15[a]	76 ± 14[a]	71 ± 15[a]	70 ± 15
PCWP (mm Hg)					
Group 1	11 ± 5	10 ± 3	17 ± 6[a,b]	8 ± 3	8 ± 5
Group 2	8 ± 6	7 ± 6	10 ± 7[b]	8 ± 6	6 ± 3[a]
Group 3	7 ± 4	7 ± 4	8 ± 4	8 ± 6	7 ± 5
Cardiac index (L·min^{-1}·m^{-2})					
Group 1	3.7 ± 1.0	3.3 ± 1.2[a]	3.4 ± 1.3[a]	3.8 ± 1.5[a,b]	3.4 ± 0.7[a]
Group 2	3.5 ± 0.7	3.1 ± 0.6[a]	3.1 ± 0.6[a]	3.3 ± 0.6	3.1 ± 0.5[a]
Group 3	3.2 ± 0.8	3.1 ± 0.6	3.1 ± 0.6	3.3 ± 0.9	3.2 ± 0.7
Stroke index (L·min^{-1}·m^{-2})					
Group 1	53 ± 11	42 ± 10[a]	42 ± 9[a]	49 ± 12[b]	47 ± 10[a]
Group 2	50 ± 10	44 ± 10[a]	43 ± 9[a]	46 ± 9[a]	46 ± 8[a]
Group 3	49 ± 13	43 ± 10[a]	42 ± 8[a]	48 ± 11	47 ± 10
Systemic arterial resistance (mmHg·L^{-1}·min^{-1}·m^{-2})					
Group 1	27 ± 11	29 ± 14	37 ± 14[a,b]	28 ± 15	28 ± 13
Group 2	29 ± 7	30 ± 8	34 ± 9[a,b]	31 ± 8	29 ± 7
Group 3	31 ± 9	24 ± 6[a]	28 ± 7[b]	24 ± 4[a]	25 ± 6[a]

All values are mean ± SD.
[a]Significant intragroup difference from baseline, $P < 0.05$.
[b]Significant intragroup difference from induction, $P < 0.05$.

Table 4. Hemodynamic Response to Infusion of Nitroglycerin and Saline in Group 3

	Mean blood pressure (mm Hg)	Heart rate (b/min)	PCWP (mm Hg)	Cardiac index (L·min^{-1}·m^{-2})	Stroke index (L·min^{-1}·m^{-2})	Systemic arterial resistance (mm Hg·L^{-1}·min^{-1}·m^{-2})
Baseline	93 ± 18	67 ± 12	7 ± 4	3.2 ± 0.8	49 ± 13	31 ± 9
After Nitroglycerin and saline[a]	88 ± 20	70 ± 13	7 ± 4	3.5 ± 0.7	52 ± 11	25 ± 7[b]

All values are mean ± SD.
Abbreviation: PCWP, pulmonary capillary wedge pressure.
[a]Nitroglycerin, 0.90 ± 0.15 μg·kg^{-1}·min^{-1}; saline, 1110 ± 398 ml.
[b]$P < 0.05$, when compared to baseline.

increases in MBP, heart rate, and PCWP at the time of laryngoscopy in such patients (2).

Because increases in systolic arterial pressure, heart rate, and PCWP are frequently involved in myocardial ischemia, we tested the effectiveness of an intravenous bolus of fentanyl, 8 μg/kg, administered 2 min prior to laryngoscopy in patients with coronary artery disease undergoing peripheral vascular surgery, most often carotid endarterectomy. Our results show that the small doses of fentanyl (3 μg/kg) used in our control group failed to prevent deleterious hemodynamic responses associated with laryngoscopy and intubation; dramatic increases in blood pressure, heart rate, and PCWP were associated with cardiac arrhythmia and ECG evidence of myocardial ischemia in four out of six patients. When the same anesthetic procedure was used in comparable patients but with larger doses of fentanyl (8 μg/kg), as in the study of Martin et al. (2), hemodynamic responses to laryngoscopy and intubation were blunted, but the frequency of cardiac arrhythmias was not significantly reduced. Marked elevation in PCWP remained in 25% of the patients and ECG evidence of myocardial ischemia still occurred in 10% of the patients during laryngoscopy and intubation. Therefore, despite attenuation of the hypertensive response to laryngoscopy and intuba-

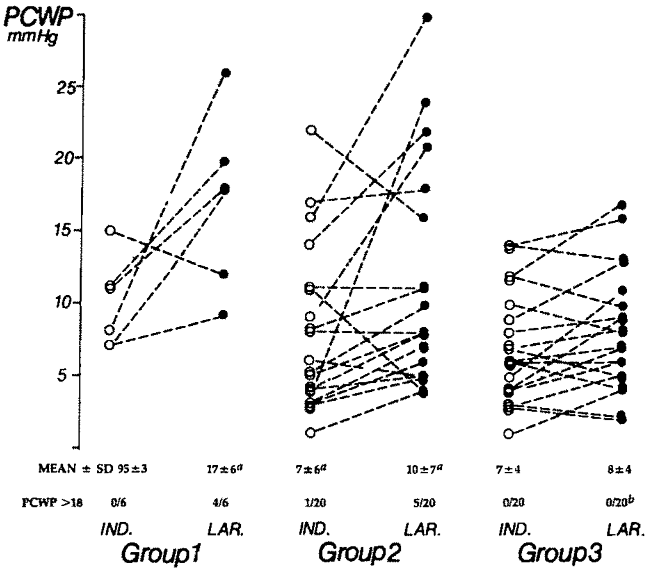

Figure 3. Individual variations in PCWP between the end of induction (IND.) and laryngoscopy (LAR.) in the three groups. As only 1 min separates these two points, these variations in PCWP may be assumed to represent the reactivity to laryngoscopy-induced stress. The first line below the figure represents mean values. $^aP < 0.05$. The second line below the figure represents the number of patients with a sustained abnormal increase in PCWP in each group. $^bP < 0.05$ when compared to corresponding frequencies in both groups 1 and 2. Nitroglycerin enables a more reliable prevention of laryngoscopy-induced marked increase in PCWP than the low-dose fentanyl methods.

tion, increasing the dose of fentanyl to 8 μg/kg failed to significantly reduce ischemia during anesthetic induction and laryngoscopy with intubation in patients with coronary artery disease undergoing relatively short peripheral vascular operations. When nitroglycerin infusion was used in addition to the smallest doses of fentanyl, the objective was to prevent hypovolemia and tachycardia-induced hypotension, because a majority of the patients we evaluated had normal baseline levels of PCWP and no ventricular failure. To fulfill this condition, anesthetic induction in group 3 implies a significant increase in the amount of intravenous solution infused (+677 ml) as compared to group 1. However, no pulmonary edema occurred during the anesthetic, surgical, or postoperative periods in any of patients and, indeed, marked increases in PCWP were more frequent in group 2 than in group 3 during laryngoscopy and intubation. Sustained expansion of blood volume in group 3 was accompanied by no change in PCWP and no significant increase in heart rate after nitroglycerin infusion, 0.9 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$, prior to anesthetic induction. A slight and insignificant decrease in blood pressure at this point was probably related to a decrease in SAR observed with this dose of nitroglycerin. During anesthetic induction, the increase in heart rate from the baseline was no more marked in group 3 than in group 1. Comparison of groups 1 and 3 shows that the addition of nitroglycerin to light narcotic analgesia inhibits an abnormal increase in MBP and PCWP that otherwise occurs during laryngoscopy and intubation, and also effectively prevents development of ECG evidences of myocardial ischemia. Nevertheless, the frequency of cardiac arrhythmias was not reduced by nitroglycerin, and there was no significant difference in the incidence of myocardial ischemia in groups 3 and 2. Evaluation of responses to painful stimulation by comparing cardiovascular data at the end of anesthetic induction and after laryngoscopy and intubation indicates that fentanyl, 8 μg/kg, provides stability in heart rate, and nitroglycerin provides stability of PCWP, but blood pressure significantly increased after laryngoscopy and intubation in the three groups. Thus none of these methods successfully prevent the hemodynamic consequences of laryngoscopy-induced painful stimulation.

An abnormal increase in the A-C wave was observed during ST changes in one group 2 patient (Fig. 2). This abnormality in the wedge pressure tracing is similar to that reported by Kaplan and Wells (12) as an early sign of myocardial ischemia during anesthesia. It is thought to be induced by a change in left ventricular compliance during myocardial ischemia. Such acute alteration in left ventricular compliance can induce discrepancies between end-diastolic left ventricular pressure and PCWP (13,14), because abnormalities in V or A-C waves are not constant on PCWP tracing during left ventricular myocardial ischemia. Thus PCWP measurements could have underestimated end diastolic left ventricular filling pressure in our study. Giles et al. (15), using radionuclide evaluation of ejection fraction, demonstrated that the magnitude of left ventricular dysfunction during laryngoscopy and intubation may not be revealed by conventional hemodynamic monitoring. However, Borer et al. (16) showed that nitroglycerin reduced exercise-induced regional wall abnormalities and increased ejection fraction attained during exercise; whether nitroglycerin may have a comparable beneficial effect during laryngoscopy and intubation in presently unknown. As ejection fraction was not evaluated during laryngoscopy and intubation in our study, a conclusion could not be reached as to the prevention of left ventricular dysfunction during laryngoscopy and tracheal intubation.

In conclusion, our findings indicate that in patients with stable angina undergoing noncardiac surgery, prophylactic continuous infusion of nitroglycerin is a reliable method for prevention of increases in blood pressure and PCWP and ST segment depression associated with laryngoscopy and intubation. In addition, it is confirmed that an intravenous bolus of "smaller" doses of fentanyl (8 μg/kg) can effectively blunt laryngoscopy-induced marked increase in blood pressure, as previously shown in vascular hypertensive patients. However, this method does not reliably prevent increases in PCWP and myocardial ischemia in patients with coronary artery disease. Finally, addition of nitroglycerin by infusion at a rate of 0.9 $\mu g \cdot kg^{-1} \cdot min^{-1}$ to low-dose fentanyl anesthesia is an attractive method for induction and for decreasing the incidence of myocardial ischemia associated with laryngoscopy and intubation in patients with stable angina undergoing short-duration noncardiac surgery.

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Bupivacaine for Intercostal Nerve Blocks in Children:

Blood Concentrations and Pharmacokinetics

Peter Rothstein, MD, G. Richard Arthur, PhD, Hal S. Feldman, BSc, Gary S. Kopf, MD, and Benjamin G. Covino, PhD, MD

ROTHSTEIN P, ARTHUR GR, FELDMAN HS, KOPF GS, COVINO BG. Bupivacaine for intercostal nerve blocks in children: blood concentrations and pharmacokinetics. Anesth Analg 1986;65:625–32.

A pharmacokinetic evaluation of bupivacaine was carried out after intercostal nerve blocks performed on 28 occasions in 27 children varying in age from 3 months to 16 yr. Bupivacaine HCl, 0.5%, with epinephrine 1:200,000 was employed. Doses of 2 mg/kg, 3 mg/kg, and 4 mg/kg resulted in peak whole blood arterial bupivacaine (base) concentrations (mean ± SD) of 0.77 ± 0.25 μg/ml, 1.37 ± 0.23 μg/ml, and 1.87 ± 0.53 μg/ml, respectively. Calculated pharmacokinetic parameters (mean ± SD) were the following: apparent volume of distribution ($V_D\beta$), 2.8 ± 0.8 L/kg; steady-state volume of distribution (V_Dss), 2.7 ± 0.7 L/kg; elimination half-life ($t_{1/2}\beta$), 147 ± 80 min; and total body clearance (Cl), 16.0 ± 7.4 $ml \cdot min^{-1} \cdot kg^{-1}$, or 382 ± 201 $ml \cdot min^{-1} \cdot m^{-2}$. Compared with data reported for adult patients, our data indicate that the volume of distribution is greater and clearance is more rapid in children than in adults. The absorption of local anesthetic from the intercostal space appears to be more rapid in children than adults. In an additional group of 11 children, the relationship of the bupivacaine blood:plasma concentration ratio (λ) to hematocrit was investigated. Hematocrit in this group ranged from 30 to 59, and λ varied from 0.47 to 0.82. There was a significant relationship between λ and hematocrit defined by the equation $\lambda = -0.0079\ Hct + 1.028$ ($r = 0.72$, $P < 0.05$). Reporting bupivacaine concentration in terms of plasma concentration may introduce an artifact that is dependent on the hematocrit, and we therefore suggest that whole blood concentration values be reported by investigators in the future.

Key Words: ANESTHETICS, LOCAL—bupivacaine. ANESTHESIA—pediatric. ANESTHETIC TECHNIQUES, REGIONAL—intercostal block.

The use of regional anesthetic techniques in children has been limited compared with their use in adults. As a result of this lack of experience and the restrictions on investigations in children, information regarding the pharmacology of local anesthetic agents in children is extremely scarce. Eyres et al. reported peak venous plasma concentrations of lidocaine in children after caudal, subcutaneous, and topical application to mucous membranes, and of bupivacaine after caudal and subcutaneous administration (1,2). Pharmacokinetic analysis of lidocaine after administration of large doses of the viscous formulation to two children have been reported (3). The pharmacokinetics and metabolism of lidocaine and mepivacaine administered subcutaneously to newborns have been investigated (4,5). However, the distribution and metabolism of local anesthetics in the newborn may not be indicative of the situation in older children due to immature hepatic and renal function in the former group (6).

Bupivacaine is a long-acting local anesthetic agent that has been employed in adults for intercostal nerve blocks for anesthesia during surgery, and for analgesia after surgery. The current study was carried out to determine the relationship of the dose of bupivacaine for intercostal nerve block to the observed blood concentration, and also to accumulate pharmacokinetic data concerning local anesthetics in children.

Methods

Intercostal nerve blocks were performed on 28 occasions in 27 children after elective cardiovascular surgery performed through a thoracotomy incision. The population characteristics of the individual patients are shown in Table 1. All children received halothane as the primary anesthetic for their surgical procedure.

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Address correspondence to Dr. Rothstein, Box 62, Babies Hospital, 622 West 168th Street, New York, NY 10032.

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Table 1. Individual Patient Characteristics and Pharmacokinetic Parameters

Bupivacaine dose	Patient number	Age (Yr)	Procedure	Weight (kg)	Peak concentration (μg/ml)	$V_D\beta$ (L/kg)	V_Dss (L/kg)	Cl/kg (ml·min^{-1}·kg^{-1})	Cl/m^2 (ml·min^{-1}·m^{-2})	$t_{1/2}\beta$ (min)
2 mg/kg										
	1	7 1/12	PDA	17	0.98	3.8	3.5	9.6	227	272
	2	14 7/12	Vasc ring	55	0.75	3.0	2.9	5.2	185	398
	3	1 7/12	PDA	10.6	0.58	3.5	3.4	23.1	471	105
	4	5/12	LLL seq	6	1.23	1.2	1.2	9.3	150	96
	5	7 10/12	PDA	30	0.65	4.2	4.0	32.0	914	91
	6	1 1/2	PDA	10	0.55					
	7	2 2/12	PDA	12.3	0.67					
3 mg/kg										
	8	2 5/12	PDA	11.6	1.05	2.6	2.6	25.3	524	71
	9	6 11/12	Coarc	22	1.36	2.4	2.4	10.0	256	165
	10	16	B-T Shunt	60	1.50	2.3	2.2	8.5	309	187
	11[a]	7 5/12	Coarc	24.5	1.28	2.3	2.3	17.8	479	90
	11[a]				1.65					
4 mg/kg										
	12	10 11/12	Coarc	33	1.20	3.8	3.5	22.2	648	119
	13	8 2/12	Coarc	27	1.03	3.7	3.5	20.9	564	122
	14	7 2/12	Coarc	25	1.96	2.8	2.5	15.5	372	126
	15	5	Coarc	19	1.75	3.1	2.7	12.3	300	173
	16	4 1/12	Coarc	17	1.89	1.9	1.9	13.0	316	98
	17	1 4/12	PDA	12	2.36	3.4	2.9	13.0	284	182
	18	5/12	PDA	5.8	1.79	3.2	2.9	19.7	258	114
	19	6/12	Coarc	6.8	1.55	3.3	3.1	20.0	389	115
	20	2 5/12	PDA	12	3.20	1.4	1.4	4.1	89	244
	21	6 7/12	Coarc	20	1.85	2.8	2.4	25.7	643	75
	22	3/12	B-T shunt	5.2	2.05	2.1	2.1	14.2	255	102
	23	4 6/12	A-V canal	14	1.37	—	—	—	—	—
	24	7 5/12	PDA	22	2.02	—	—	—	—	—
	25	4 7/12	Coarc	16	1.38	—	—	—	—	—
	26	1 3/12	PDA	9.6	2.19	—	—	—	—	—
	27	1	PDA	7.6	2.39	—	—	—	—	—

Abbreviations: PDA, patent ductus arteriosus ligation; Vasc ring, division of vascular ring; LLL seq, resection of sequestered left lower lobe; Coarc, resection of coarctation of the aorta; B-T shunt, creation of a Blalock-Taussig shunt; A-V canal, repair of atrioventricular canal and sequestered right lower lobe; $V_D\beta$, apparent volume of distribution; V_Dss, steady-state volume of distribution; Cl, total body clearance; $t_{1/2}\beta$, elimination half-life.

[a] Patient 11 had nerve blocks performed on two occasions.

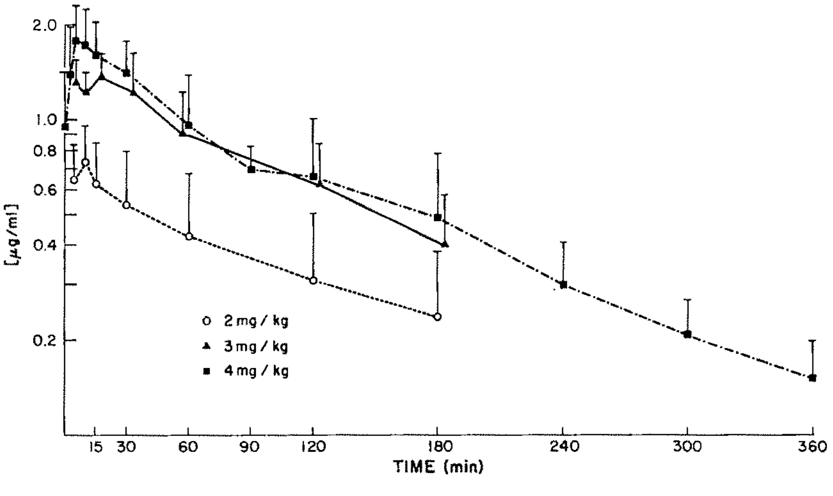

Figure 1. Arterial whole blood concentration of bupivacaine (µg/ml) as a function of time at the three doses employed. Mean values and standard deviations are indicated. For clarity, points at 2 and 4 min have been omitted in the 4 mg/kg group.

After skin closure and before awakening and tracheal extubation, the nerves in five intercostal spaces were blocked with bupivacaine hydrochloride, 0.5%, with epinephrine, 1:200,000. Doses of 2 mg/kg, 3 mg/kg, or 4 mg/kg were injected. Epinephrine was added to the bupivacaine solutions immediately before performance of the block. In one case, nerve blocks were performed while the child was awake in the intensive care unit. Nerve blocks were performed during continuous electrocardiographic and direct intraarterial blood pressure monitoring. Samples of arterial blood for measurement of bupivacaine concentrations were obtained from indwelling radial artery catheters immediately before performing the nerve blocks and 5, 10, 15, 30, 60, 120, and 180 min after completion of the block in children who received 2 mg/kg and 3 mg/kg of bupivacaine. In children who received 4 mg/kg of bupivacaine, additional samples were drawn at 1, 2, 3, 4, 240, and 360 min. Each sample was 1.5 ml. Because of limitations on the volume of blood that could be safely obtained from the children, several patients did not have samples obtained at each time interval. Central venous and peripheral arterial samples were simultaneously obtained from four children who received 3 mg/kg and from five children who received 4 mg/kg to evaluate uptake of bupivacaine by the lung. Four children who had indwelling urinary catheters had all urine collected for 24 hr after completion of the nerve blocks. Urine was analyzed for unmetabolized bupivacaine.

Heparinized blood samples and urine specimens were frozen at −20°C until analyzed. Bupivacaine (base) concentration in whole blood was assayed by a gas chromatographic technique similar to that reported by Tucker (7). The coefficient of variation of this technique in our laboratory was ±5% at a concentration of 0.5 µg/ml.

Arterial whole blood bupivacaine concentration data were subjected to pharmacokinetic analysis using model-independent techniques. Model-independent analysis was based on the methods described by Tucker (8). Area under the drug concentration curve (AUC) and area under the moment curve (AUMC) were determined using the trapezoidal rule with extrapolation to infinity. Other measured pharmacokinetic variables included: total body clearance (Cl) = dose/AUC; half life of elimination ($t_{1/2}\beta$) = $0.693/\beta$, where β is the slope of the elimination phase determined by linear regression analysis of the bupivacaine concentration data versus time occurring post absorption/distribution of drug; steady-state volume of distribution (V_Dss) = dose·AUMC/AUC^2; apparent volume of distribution based on the elimination phase ($V_D\beta$) = dose/AUC·β; mean body residence time (MBRT) = AUMC/AUC indicating the average time drug molecules remain in the body.

To determine the effect of hematocrit on the whole blood:plasma concentration ratio, λ, blood was obtained after induction of anesthesia in a separate group of 11 children undergoing cardiac surgery. Hematocrits in this group ranged from 30 to 59. Samples were heparinized, a known amount of bupivacaine added, and samples incubated for 20 min at 37°C. After an aliquot was obtained for determination of whole blood bupivacaine concentration, the sample was centrifuged, plasma removed, plasma bupivacaine concentration determined and λ calculated for each sample.

All data are reported as mean ± SD. The relationship of dose to time of peak concentration was examined by χ^2 analysis with Yates's correction applied. Comparison of pharmacokinetic variables at different doses was performed by analysis of variance. The relationship of pharmacokinetic variables to weight and surface area and the effect of hematocrit on λ was

Table 2. Peak Arterial Whole Blood Bupivacaine Concentration and Frequency of Occurrence at Given Sampling Times

Bupivacaine dose (mg/kg)	Mean peak concentration ± SD (μg/ml)	Frequency of occurrence				
		<5 min	5 min	10 min	15 min	30 min
2	0.77 ± 0.25		1	5	1	
3	1.37 ± 0.23		1	2	1	1
4	1.87 ± 0.53	1	9	4	2	

determined by linear regression analysis. Values of $P < 0.05$ were considered significant. These studies were approved by the Yale University School of Medicine Human Investigation Committee, and parental consent was obtained.

Results

Arterial whole blood concentrations (μg/ml) of bupivacaine after the intercostal administration of 2–4 mg/kg of this agent are depicted in Figure 1. Peak blood concentrations occurred 5–15 min after performance of the intercostal block (Table 2). The mean peak concentration of bupivacaine for the three groups varied from 0.77 ± 0.25 μg/ml in patients receiving 2 mg/kg of bupivacaine to 1.37 ± 0.23 μg/ml in patients receiving 3 mg/kg, and 1.87 ± 0.53 μg/ml in the children receiving 4 mg/kg of anesthetic agent. The dose of bupivacaine administered affected the rapidity with which the peak concentration was obtained. Compared with children receiving 2 and 3 mg/kg, there was a significant difference ($P < 0.05$) between the number of children whose peak concentration occurred at or before 5 min and those whose peak occurred after 5 min when the dose employed was 4 mg/kg.

Adequate data points were available for 20 children for the calculation of various pharmacokinetic parameters (Table 1). Because of the large patient weight range, data have been presented on a per-kilogram basis where appropriate. In all cases, 100% absorption of drug was assumed. The elimination half-life was 147 ± 80 min. The apparent volume of distribution was 2.8 ± 0.8 L/kg, with a very similar steady-state volume of distribution of 2.7 ± 0.7 L/kg. The clearance of bupivacaine was 16.0 ± 7.4 $\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ or 382 ± 201 $\text{ml}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$. Mean body residence time (MBRT) was 202 ± 111 min. Clearance was not related to either patient weight or surface area.

Differences between peripheral arterial and central venous concentrations of bupivacaine determined in nine children are shown in Figures 2 and 3. Children receiving 3 mg/kg (Fig. 2) consistently had higher concentrations of bupivacaine in peripheral arterial blood than in central venous blood soon after completion of the nerve block, implying initial uptake and then release of drug by the lung. Somewhat different findings were observed in children given 4 mg/kg (Fig. 3). Two children had higher peripheral arterial concentrations, though the difference between arterial and central venous levels was less than in children given 3 mg/kg. One child demonstrated no difference. Two children demonstrated central venous bupivacaine concentrations that were greater than peripheral arterial concentrations, possibly implying continued uptake of drug by the lung in these children.

The effect of hematocrit on λ is shown in Table 3. The relationship of λ to hematocrit is defined by the regression equation $\lambda = -0.0079 \text{ Hct} + 1.028$. The correlation coefficient for the data is 0.72 and is statistically significant ($P < 0.05$).

During the first 24 hr after intercostal nerve blockade, 0.69% (range 0.35–1.13%) of the injected dose of bupivacaine was recovered in the urine as unchanged drug.

Discussion

The vascular absorption of local anesthetic agents from the site of injection occurs more rapidly after intercostal nerve blockade than it does with the other regional anesthetic techniques (9). Willdeck-Lund and Edström, for example, studied the absorption of bupivacaine, 0.5%, with epinephrine 1:200,000 after intercostal block in adults (10). Nerve blocks were performed at the conclusion of thoracotomy, with the chest open. Two milliliters of drug was injected into each of seven intercostal spaces (total dose = 70 mg) "as close to the spinal column as possible." Patients received halothane as their primary anesthetic. Arterial whole blood concentrations of bupivacaine peaked at 10 min after nerve block, and the mean peak concentration was approximately 0.4 μg/ml whole blood. Moore et al. reported peripheral arterial and venous plasma concentrations of bupivacaine after bilateral intercostal nerve block using bupivacaine 0.5% with epinephrine 1:320,000 (total dose = 400 mg) (11). The blocks were performed while the patients received intravenous methohexital, 100–150 mg. Peak

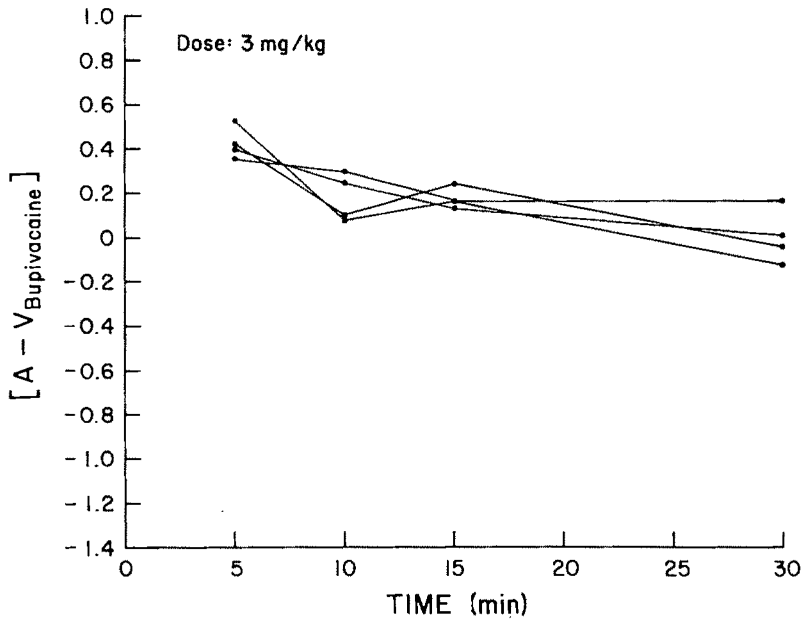

Figure 2. Differences in arterial-venous concentrations of bupivacaine in simultaneously obtained samples as a function of time after intercostal injection of 3 mg/kg. All children had higher whole blood bupivacaine concentrations in peripheral arterial blood than in central venous blood, indicating release of bupivacaine from the lung into arterial blood.

arterial concentrations occurred 10–20 min after nerve block.

In the present study, vascular uptake of bupivacaine was also rapid. The rate of absorption, as reflected by the time at which the peak arterial concentration of bupivacaine occurred, was somewhat more rapid than that previously reported in adults (10,11). The more rapid absorption of bupivacaine observed in our patients may be due, in part, to the fact that cardiac output per kilogram body weight is greater in children than in adults, which might result in an enhanced vascular perfusion in areas such as the intercostal space (12). The rate of absorption may also be related to the volume of anesthetic solution injected relative to the size of the intercostal space. In adults, 2–4 ml of anesthetic solution are usually employed for individual intercostal nerve blocks. In the present study, in children in whom 4 mg/kg of bupivacaine were used, volumes of 0.16 ml/kg were injected into each intercostal space. The range of volumes employed was 0.8–5.2 ml/interspace. Thus the local anesthetic solution may have been exposed to a relatively greater vascular surface area in our children than in studies in adults, which would enhance the rate of absorption in children. The impossibility of obtaining pharmacokinetic data for bupivacaine after intravenous infusion to a similar population of patients negates the possibility of determining the mean absorption time (MAT) of drug. (MAT = MBRT (absorption site) − MBRT (intravenous) − $t_{(lag)}$, where $t_{(lag)}$ is the time from injection to the start of drug absorption).

Children with coarctation of the aorta or lesions with right-to-left intracardiac shunts have enlarged intercostal arteries, whereas children with a patent ductus arteriosus have normal-sized intercostal arteries. The time of occurrence of peak arterial concentration of bupivacaine was similar in six children with a patent ductus arteriosus and in eight children with coarctation of the aorta, who had received 4 mg/kg. In the groups who received 2 and 3 mg/kg of bupivacaine, no tendency was observed for the children with coarctation or cyanosis to have earlier peak drug concentrations as compared with children with a patent ductus. Thus vessel size does not appear to have been a major factor in determining uptake of drug from the intercostal space.

In our study, we chose to report bupivacaine concentration in terms of μg/ml whole blood for two reasons. First, Tucker and Mather, in discussing the determination of pharmacokinetic variables of local anesthetics, stressed that peripheral tissues are exposed to the concentration of drug contained in whole blood, not just plasma (13). Second, we demonstrated that hematocrit affects λ. Thus, in two samples of whole blood with the same quantity of bupivacaine added, the plasma concentrations in the two samples vary with the hematocrit. In our pharmacokinetic study, the hematocrits ranged from 31–55 and use of plasma concentrations would have made comparisons of peak concentrations between children difficult to evaluate.

We found that λ varied between 0.47 and 0.82 in the children studied, which contrasts with the value for λ of 0.73 ± 0.05 that has been reported in adults (14). (Hematocrits of the adult subjects were not stated). If a plasma concentration is calculated from our mea-

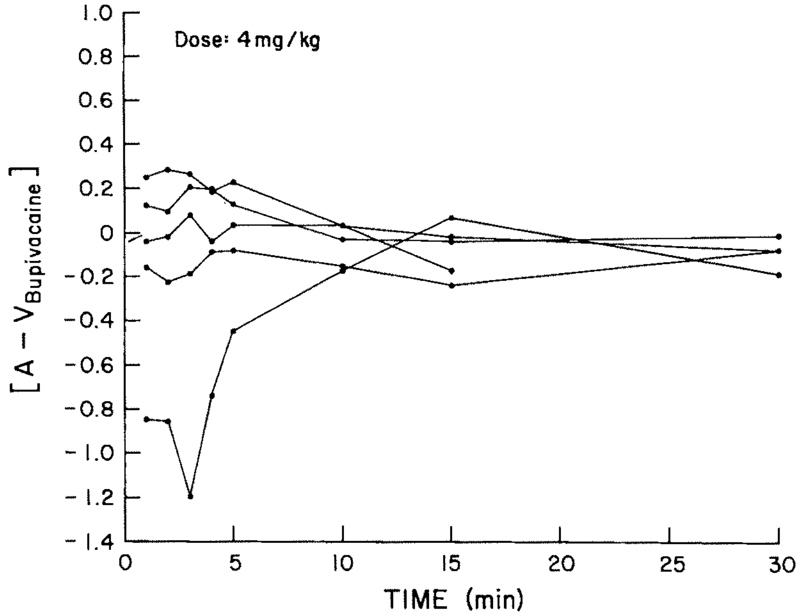

Figure 3. Differences in arterial–venous concentrations of bupivacaine plotted as in Figure 2 after injection of 4 mg/kg. Two children had concentrations greater in central venous blood than in arterial blood, possibly indicating prolonged uptake of bupivacaine by the lung.

sured values for whole blood concentration and λ determined by our regression equation, then a number of children who received 4 mg/kg may have had plasma concentrations that approached or exceeded the hypothesized toxic plasma concentration of 4 μg/ml for this agent (15). The highest whole blood concentration of bupivacaine observed in any child was 3.2 μg/ml. No cardiovascular or central nervous system toxicity was observed in this study. There may be several explanations for the lack of observed toxicity in our patients. First, the plasma concentration of 4 μg/ml as the toxic threshold for convulsions is based on speculation. In fact, there are data to suggest that this putative toxic concentration is too low (16). Second, our patients were anesthetized at the time of nerve block. However, muscle activity was possible, and seizure activity would have been visible had it occurred. It has been shown that central nervous system depressants such as diazepam, nitrous oxide, and barbiturates increase the toxic threshold of local anesthetics (17–19). All children had continuous heart rate and blood pressure monitoring during the study, and there was no evidence of cardiovascular toxicity. It should be noted that in previous studies of absorption of bupivacaine from the intercostal space, patients were anesthetized with either halothane or methohexital. Finally, but less likely, children may be less sensitive to the toxic effects of bupivacaine than adults. It has been demonstrated, however, that there are no significant differences in sensitivity to the toxic effects of local anesthetics betwen fetal, newborn, and adult sheep, and this may also be true in humans (20). Liu et al. failed to demonstrate any difference in the median convulsant dose, CD_{50} of lidocaine, chloroprocaine, bupivacaine, and etidocaine in immature and mature mice (21).

A comparison of the pharmacokinetic parameters of the bupivacaine in children, determined in this study, and values reported in adults (13) show two differences (Table 4). The volume of distribution at steady-state, V_Dss, and clearance of bupivacaine are greater in children than in adults. A larger extracellular fluid space as well as a higher proportion of well perfused tissue and lower amounts of body fat in children could be related to the greater volume of distribution in children compared to adults. Of the amide-type local anesthetics, bupivacaine has the lowest hepatic extraction value (0.31) (13), implying that bupivacaine clearance values are less likely to be affected by changes in hepatic blood flow. However, the high clearance values determined in this study may be partially due to a greater hepatic blood flow per kg in children than in adults. The elimination half-life of bupivacaine in both children and adults was similar (147 and 156 min).

Our calculations assumed 100% absorption of drug. Incomplete absorption would tend to overestimate the V_Dss and clearance values we obtained. Our values for these parameters are 2.7 and 2.4 times, respectively, the values reported in adults. We doubt that these differences are solely on the basis of drug absorption since one would then have to postulate that only approximately ⅓–½ of the injected drug was absorbed from a site that has a very rapid absorption of the agent.

In four patients (numbers 1, 2, 10, and 20) the $t_{½}β$

Table 3. Effect of Hematocrit on Whole Blood/Plasma Concentration Ratio (λ)

Patient	Hematocrit	Bupivacaine base μg/ml Whole blood	Plasma	λ
1	32	2.13	2.71	0.79
2	35	2.07	2.67	0.78
3	30	1.86	2.28	0.82
4	39	1.23	1.85	0.66
5	33	1.47	1.80	0.82
6	34	1.71	2.52	0.68
7	50	1.84	2.95	0.62
8	59	1.76	2.88	0.61
9	50	1.23	2.62	0.47
10	49	1.88	2.45	0.77
11	53	1.74	2.84	0.61

Table 4. Pharmacokinetics of Bupivacaine in Children and a Comparison with Data Obtained after Intravenous Infusion in Adults (13)

Parameter	Children	Adults
$t_{1/2}\ \beta$ (min)	147 ± 80	156 ± 66
$V_D\beta$ (L/kg)	2.8 ± 0.8	
V_Dss (L/kg)	2.7 ± 0.7	1.0[a]
Cl ($ml \cdot min^{-1} \cdot kg^{-1}$)	16.0 ± 7.4	6.7[a]
MBRT (min)	202 ± 111	126[b]
AUC ($\mu g \cdot ml^{-1} \cdot min^{-1}$)	235 ± 169	
AUMC ($\mu g \cdot ml \cdot min^{-2}$)	57097 ± 70343	
Dose (mg base)	58.6 ± 38.2	66.6
Weight (kg)	21.0 ± 15.0	(70)

Abbreviations; $t_{1/2}\beta$, elimination half-life; $V_D\beta$, apparent volume of distribution; V_Dss, steady-state volume of distribution; Cl, total body clearance; MBRT, mean body residence time; AUC, area under the drug concentration curve; AUMC, area under the moment curve.

[a] Calculated from reference 13 assuming patient weight was 70 kg.

[b] Reference 8.

was greater than the sampling period. Ideally, in a pharmacokinetic study one would want the sampling time to be at least twice the $t_{1/2}\beta$. In our studies, we were limited in the amount of blood that we could obtain and therefore initially limited our sampling period to 180 min. When we analyzed samples from the initial studies and found that $t_{1/2}\beta$ values approached our longest sampling time, we were able to extend our sampling time to 360 min. The $t_{1/2}\beta$ for patients with the sampling time period of 180 min is not significantly different from the value for patients with a sampling period of 360 min.

The uptake of local anesthetics by the lung is considerable, but transient (22). Uptake of local anesthetics can be demonstrated by the comparison of their concentration in simultaneously obtained peripheral arterial and mixed venous blood samples. During pulmonary uptake, the peripheral arterial concentration will be less than the central venous concentration. If the lung takes up drug and then releases it back into the circulation, during the time that drug is being released the peripheral arterial concentration will be greater than the central venous concentration. Uptake of local anesthetic by the lung has been observed clinically after intravenous regional anesthesia and intercostal nerve blockade as well as in laboratory experimental studies (11,23). Similar observations were made in the present pediatric population. Children given 3 mg/kg of bupivacaine had very rapid lung uptake and subsequent release of drug back into the blood, because the arterial concentration exceeded the central venous concentration of bupivacaine in our earliest samples, obtained at 5 min. The findings in the children receiving 4 mg/kg were unexpected and require explanation. Two children demonstrated arterial concentrations greater than the venous concentration, implying release of drug from the lung. This was qualitatively similar to the findings in the 3 mg/kg group, though the differences were quantitatively less. One child had no difference between specimens implying no net transfer of drug, i.e., uptake and release were equal. Two children had venous concentrations that were greater than arterial concentrations, implying continued uptake of drug by the lung. Our venous samples were obtained from the superior vena cava or right atrium, and would tend to overestimate the amount of bupivacaine in the mixed venous blood, because mixed venous samples also contain a contribution from the inferior vena cava, which has a lower concentration of bupivacaine because of hepatic clearance of the drug. However, with the exception of samples obtained across the lung, venous specimens have never been demonstrated to contain more local anesthetic than arterial specimens, and thus a sampling artifact in our study could not account for the finding of prolonged lung uptake of bupivacaine. This overestimation of venous bupivacaine content could explain the lack of uptake seen in one patient. One explanation for the finding of possible prolonged uptake of drug by the lung in two patients was that the lung's capacity for local anesthetic was markedly increased due to unknown factors. Another explanation is also speculative. Four of the five children who received 4 mg/kg had been treated with intravenous propranolol (0.1–0.2 mg) for the control of hypertension 1–2 hr prior to performance of the nerve blocks. The 4 mg/kg group had a higher percentage of children with coarctation than the 3 mg/kg group, which accounts for the use of propranolol only in one group. Propranolol is taken up by the lung (24). Propranolol is also a potent inhibitor of the pulmonary uptake of bupivacaine (25). If pulmonary binding sites are occupied by propranolol, the degree of initial lung uptake of local anesthetic may be decreased. The local anesthetic may then gradually displace propranolol. Thus, rather than a large rapid uptake of local anesthetic by the lung, followed by its release from lung tissue, a slow, prolonged uptake of small amounts of local anesthetics may occur in the presence of propranolol.

Our investigation indicates differences in the uptake and disposition of local anesthetic in children and adults. The absorption of local anesthetic from the intercostal space appears to be more rapid, clearance of bupivacaine is more rapid, and volume of distribution is greater in children than in adults.

The results of this study indicate that bupivacaine in doses of 2–4 mg/kg could be employed for intercostal nerve blockade in children under general anesthesia without demonstrable side effects. Because drug uptake from the intercostal space appeared to be dose-dependent, and occasional blood concentrations of drug of greater than 3.0 μg/ml were found when a dose of 4 mg/kg was employed, a greater margin of safety with the drug could be obtained if a dose of no larger than 3 mg/kg is used.

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Hemodynamic Effects of Isoflurane in the Newborn Piglet:

Comparison with Halothane

Richard A. Schieber, MD, Anne Namnoum, BA, Anne Sugden, BS, Gerald K. Shiu, PhD, Richard A. Orr, MD, and D. Ryan Cook, MD

SCHIEBER RA, NAMNOUM A, SUGDEN A, SHIU GK, ORR RA, COOK DR. Hemodynamic effects of isoflurane in the newborn piglet: comparison with halothane. Anesth Analg 1986;65:633–8.

To better understand the mechanism of hypotension and bradycardia that may occur in newborn infants during isoflurane anesthesia, we studied the hemodynamic changes in the major determinants of cardiac output in 15 newborn piglets given 0.5, 1.0, and 1.3 minimal alveolar concentrations (MAC) of isoflurane and in nine sham-instrumented, age-matched control animals. Cardiac output did not differ from the baseline reading or the control group at any isoflurane dose. Mean aortic pressure (MAP) decreased 23–45% in a dose-related manner. Total peripheral resistance index (TPRI) decreased 29% at 0.5 MAC, but did not decline further at higher concentrations. Because the decrease in MAP was offset by a similar reduction in TPRI, cardiac output did not change. Heart rate decreased significantly at 1.3 MAC (−19%). Contractility was depressed at all concentrations: left ventricular dP/dT decreased progressively at 0.5 and 1.0 MAC, and echocardiographic shortening fraction decreased significantly at 1.0 MAC. Left ventricular end-diastolic pressure was not affected. Eight of twelve animals who had bradycardia while breathing isoflurane were atrially paced at their baseline heart rate. Because pacing did not restore MAP, TPRI, and LV dP/dT/DP40 (a contractile index independent of preload and afterload) to control values, bradycardia was not primarily responsible for depression of these variables. At equipotent concentrations, isoflurane reduced MAP and TPRI more than, and cardiac output less than, halothane did in previous studies in this laboratory. Heart rate and dP/dT were decreased to a similar extent by both agents. Blood, heart, and brainstem isoflurane LD:MAC ratios were 2.04, 2.00, and 2.84, respectively, indicating a relatively low margin of safety for isoflurane in young piglets.

Key Words: ANESTHETICS, VOLATILE—isoflurane. HEART—myocardial function. ANESTHESIA—pediatric.

During induction of anesthesia in infants, isoflurane causes moderately severe bradycardia and hypotension, which cannot be completely ameliorated by atropine (1). To better understand the mechanism of these adverse effects, we studied the dose–response relationship of isoflurane to cardiac output and its principal determinants—preload, afterload, heart rate, and contractility—in healthy newborn piglets. We also compared the magnitude of hemodynamic effects caused by isoflurane with the magnitude of the effects of an equipotent dose of halothane in other newborn piglets, as reported in an earlier study in this laboratory (2). In addition, we determined the margin of safety of isoflurane in newborn piglets.

Methods

Animal Preparation

Twenty-four healthy farm piglets, age 2–17 (mean 9) days, weighing 1.28–4.17 (mean 2.28) kg, were studied using a protocol approved by our institutional review board. These animals were divided into an isoflurane and a control group: hemodynamic studies were conducted on 15 animals who received isoflurane, while nine control animals were age-matched and sham-instrumented but received no isoflurane. The hemodynamic variables of each control animal were recorded at the same time intervals as those of its matched isoflurane animal. All animals were tra-

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Address correspondence to Dr. Schieber, Henrietta Egleston Hospital for Children, Emory University School of Medicine, 1405 Clifton Rd., N.E., Atlanta, GA 30322.

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cheally intubated and vascular catheters were inserted under local analgesia. The animals were maintained as described in a previous study (2). Controlled mechanical ventilation was used to maintain eucapnea during the experiment, and was facilitated with metocurine during instrumentation. Ventilation was delivered through a modified circle circuit that permitted accurate measurement of end-tidal gas concentrations by mass spectrometry (3). Oxygen was the carrier gas. Intravenous 5% dextrose in 0.2N saline was provided at 4 $ml \cdot kg^{-1} \cdot hr^{-1}$, including bolus thermodilution injections.

MAC and Hemodynamic Studies

In a pilot study of five sibling newborn piglets not used for the hemodynamic studies, the minimal alveolar concentration (MAC) requirements generally increased with age when isoflurane was administered once or twice weekly during the first 3 weeks of life (Fig. 1). Because of the intrasubject variability and increased MAC at older ages, we could not assume that MAC was constant for all animals studied. Instead, we determined isoflurane MAC for *each animal* prior to beginning the hemodynamic study, waiting at least 1 hr after instrumentation had been completed to allow most neuromuscular function to return. For the evaluation of MAC, isoflurane was initially administered in 0.5% end-tidal increments. After 15 min at each concentration, the tail and a toe were clamped for 30 sec and the animal observed for limb movement. If no movement occurred, the end-tidal concentration was reduced in 0.1% decrements until a positive response was elicited. Mean alveolar concentration, the effective anesthetic concentration, was defined here as the concentration midway between the lowest end-tidal concentration at which the animal had a negative motor response and the highest end-tidal concentration at which it had a positive response (4).

During the hemodynamic studies, heart rate, cardiac output, mean aortic pressure (MAP), left ventricular end-diastolic pressure (LVEDP), LV peak dP/dT, LV echocardiographic shortening fraction (SF), total peripheral resistance index (TPRI), and stroke volume index (SVI) were all measured or calculated as described in an earlier study (2). LV dP/dT/DP40, the dP/dT point measurement 40 mm Hg above LVEDP, was measured at baseline and at each dose of isoflurane. Left ventricular dP/dT/DP40 was also measured before and during right atrial pacing at the baseline heart rate in an effort to isolate changes in contractility from changes in heart rate, preload, and afterload.

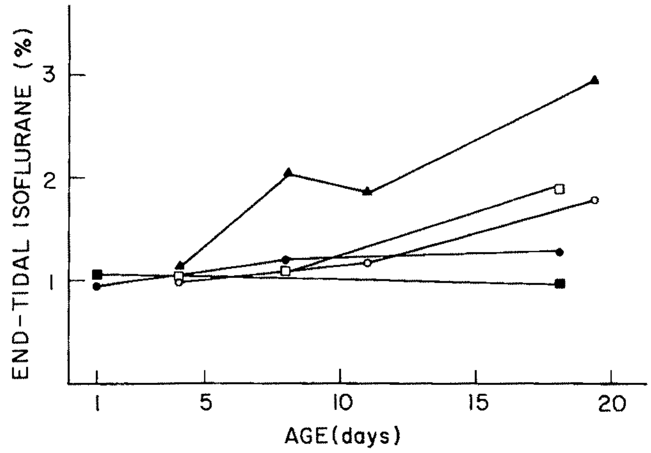

Figure 1. MAC vs age for five sibling newborn piglets. Each line represents one animal studied repeatedly during the first 3 weeks of life.

Baseline hemodynamic variables were recorded before any isoflurane was administered. A data set was then recorded sequentially at 1.3, 1.0, and 0.5 MAC. Each concentration was maintained for 15 min before hemodynamic measurements were made. If the heart rate decreased more than 10% from its baseline value at any concentration, another hemodynamic profile was recorded after 5 min of atrial pacing at the baseline heart rate.

Isoflurane hemodynamic values are expressed as mean ± SD. Data were subjected to one-way analysis of variance and Student–Newman–Kuels multiple range test to determine the statistical significance of differences in the mean values of each variable at all isoflurane concentrations. These tests were also used to compare isoflurane data with the corresponding control group values (5). The significance level for the experiment (α) was 0.05.

The hemodynamic effects of isoflurane at 1.3 MAC were compared with those seen with 1.0% end-tidal halothane (1.3 MAC) in another group of 11 piglets we previously studied (2). Unpaired Student's t-test was used to describe differences in baseline values between the two anesthetic groups. To adjust for any such baseline differences, the baseline reading for each variable was subtracted from its value at 1.3 MAC to express isoflurane data as a percent change from baseline. Unpaired t-tests were then used to analyze these percent changes; significance was assumed if $P < 0.05$.

Margin of Safety Study

In 12 other newborn piglets 1–13 days old, we obtained arterial blood, atrial, and/or brainstem samples at MAC and/or the lethal isoflurane concentration.

Table 1. Hemodynamic Effects of Isoflurane

	Baseline	0.5 MAC	1 MAC	1.3 MAC
Cardiac output (L·min^{-1}·kg^{-1})	0.263 ± 0.039^{a,b}	0.293 ± 0.051^{a} (+11%)	0.251 ± 0.039^{a,c} (−5%)	0.225 ± 0.042^{b,c} (−14%)
MAP (mm Hg)	120 ± 23^{a}	92 ± 20^{b,*} (−23%)	76 ± 16^{c,*} (−37%)	66 ± 15^{c,*} (−45%)
Heart rate (beats/min)	194 ± 43^{a}	187 ± 41^{a} (−4%)	164 ± 22^{a,c} (−15%)	157 ± 24^{b,c*} (−19%)
dP/dT (mm Hg/sec)	3547 ± 843^{a}	2360 ± 577^{b,*} (−33%)	1827 ± 328^{c,*} (−48%)	1573 ± 433^{c,*} (−56%)
dP/dT/DP40 (mm Hg/sec)	2560 ± 519^{a}	2040 ± 448^{b,*} (−20%)	1733 ± 327^{c,*} (−32%)	1480 ± 319^{c,*} (−42%)
Shortening fraction (%)	40 ± 10^{a,*}	35 ± 8^{a,b} (−13%)	32 ± 9^{b,c} (−20%)	28 ± 7^{c,*} (−30%)
TPRI (mm Hg·L^{-1}·min^{-1}·kg^{-1})	444 ± 137^{a}	314 ± 77^{b,*} (−29%)	303 ± 79^{b,*} (−32%)	298 ± 73^{b,*} (−33%)
SVI (ml·beat^{-1}·kg^{-1})	1.5 ± 0.5^{a}	1.7 ± 0.4^{a} (−13%)	1.7 ± 0.4^{a} (−13%)	1.6 ± 0.3^{a} (−7%)
LVEDP (mm Hg)	4.0 ± 3.4^{a}	2.9 ± 2.8^{a}	4.7 ± 1.7^{a}	4.5 ± 1.8^{a}

All values are mean ± SD.

Abbreviations: MAP, mean aortic pressure; TPRI, total peripheral resistance index; SVI, stroke volume index; LVEDP, left ventricular end-diastolic pressure.

Asterisk denotes significant difference from the control group, which did not receive isoflurane ($P < 0.05$). Letters in common denote *non*significant differences ($P > 0.05$). For example, the heart rates at Baseline, 0.5 MAC, and 1.0 MAC are not significantly different. Heart rate at 1.3 MAC is significantly different from baseline and 0.5 MAC but not significantly different from 1.0 MAC, denoted by the shared letter "c". 1.3 MAC is the only concentration that caused a significant difference in Heart Rate from the control group.

The lethal dose (LD) was defined as spontaneous, irrevocable, and terminal second- or third-degree heart block, because these were invariably followed shortly by ventricular standstill. If the median sternotomy or atrial biopsy at MAC caused death, samples of heart, brain, and blood could not be obtained at the "true" lethal concentration.

Tissue samples were immediately crushed, added to a preweighed aliquot of 0.02% chloroform in carbon tetrachloride, homogenized, reweighed to determine the tissue wet weight, and centrifuged to remove cellular debris. A 1 μl aliquot of supernatant was injected into a gas–liquid chromatograph equipped with a 6′ × ½″ glass 5% SE-30 column and a flame-ionization detector. The injector, detector, and column were maintained at 120, 120, and 60°C, respectively. The retention times of isoflurane and chloroform (internal standard) were 0.54 and 0.90 min, respectively. Isoflurane concentrations were determined in triplicate, as previously described, by comparing the isoflurane-to-chloroform ratio peak heights of the unknown concentration with that of isoflurane standards of known concentrations (6). Method precision was 5% and the accuracy was 4%. These were determined using a known concentration of anesthetic agent added to a known weight of unanesthetized tissue. Precision and accuracy were the coefficients of variation of the observed mean and the known standard concentration, respectively.

Results

Isoflurane MAC for these piglets was 1.20 ± 0.43% (range 0.69–1.94%). Table 1 shows the hemodynamic data for isoflurane and for control animals. With isoflurane, cardiac output did not change significantly from baseline, nor was it statistically different at any MAC fraction from that of the control group. However, MAP decreased significantly and substantially at all MAC fractions, changes not observed in the control group. Total peripheral resistance index decreased 29% at 0.5 MAC, but did not change further at higher concentrations. Heart rate changed significantly only at 1.3 MAC (−19%). Contractility was depressed at all MAC fractions. Shortening fraction decreased 20% and 30% at 1.0 and 1.3 MAC, respectively. From 0.5 to 1.0 MAC, values for dP/dT and dP/dT/DP40 decreased progressively. SVI and LVEDP did not change significantly during the study.

Twelve of 15 animals had bradycardia (heart rate change ≥ 10% of baseline) while breathing isoflurane; eight were paced. dP/dT/DP40 was measured to evaluate contractility, because it is relatively independent of changes in preload and afterload at fixed heart rates (7). One MAC isoflurane profoundly reduced dP/dT/DP40 before and after atrial pacing to a statistically similar extent (Table 2). No variable except heart rate recovered during pacing.

Table 3 shows the baseline values of the isoflurane and halothane groups. Figure 2 compares their hemodynamic response to these drugs administered at an equipotent dose, 1.3 MAC. No other equipotent dose data were available for comparison. Both agents depressed dP/dT and heart rate to a similar extent ($P > 0.05$). Cardiac output was significantly more depressed by halothane, but MAP and TPRI were more depressed by isoflurane.

Blood, atrial, and brainstem concentrations at MAC and the LD for 12 other piglets are shown in Table 4. Grouping all animals together, the ratios of mean LD-

Table 2. Hemodynamic Effects of Isoflurane before and after Pacing

	0 MAC	0.5 MAC		1.0 MAC		1.3 MAC	
		Unpaced	Paced	Unpaced	Paced	Unpaced	Paced
Cardiac output ($L \cdot min^{-1} \cdot kg^{-1}$)	0.244 ± 0.34	0.290 ± 0.05	0.293 ± 0.06	0.258 ± 0.04	0.276 ± 0.04	0.214 ± 0.04	0.241 ± 0.05
MAP (mm Hg)	131 ± 15	95 ± 21	97 ± 19	75 ± 13	76 ± 14	63 ± 6	66 ± 10
Heart rate (beats/min)	209 ± 31	204 ± 40	217 ± 30	171 ± 17	202 ± 32[a]	155 ± 20	202 ± 32[a]
dP/dT (mm Hg/sec)	3800 ± 741	2450 ± 648	2475 ± 623	1850 ± 351	1925 ± 501	1525 ± 399	1625 ± 471
dP/dT/DP40 (mm Hg/sec)	2750 ± 499	2100 ± 535	2125 ± 534	1825 ± 377	1825 ± 433	1475 ± 337	1600 ± 440
Shortening fraction (%)	42 ± 10	40 ± 6	40 ± 6	36 ± 5	34 ± 6	32 ± 6	30 ± 5
TPRI (mm Hg$\cdot L^{-1} \cdot min^{-1} \cdot kg^{-1}$)	549 ± 105	322 ± 74	337 ± 116	230 ± 56	280 ± 55	301 ± 62	278 ± 69
SVI ($ml \cdot beat^{-1} \cdot kg^{-1}$)	1.2 ± 0.2	1.5 ± 0.2	1.4 ± 0.2	1.7 ± 0.4	1.5 ± 0.5	1.5 ± 0.2	1.3 ± 0.2
LVEDP (mm Hg)	2.5 ± 2.1	2.3 ± 3.7	2.1 ± 3.6	4.4 ± 1.8	3.8 ± 1.4	4.0 ± 1.9	3.8 ± 2.0

All values are mean ± SD; n = 8.

Abbreviations: MAP, mean aortic pressure; TPRI, total peripheral resistance index; SVI, stroke volume index; LVEDP, left ventricular end-diastolic pressure.

[a] $P < 0.05$ vs unpaced value at same MAC fraction.

Table 3. Baseline Values of Piglets Given Isoflurane or Halothane

	Isoflurane (n = 15)	Halothane[a] (n = 11)
Age (days)	9.3 ± 3.8	7.5 ± 4.2
Weight (kg)	2.28 ± 0.67	2.22 ± 0.70
Cardiac output ($L \cdot min^{-1} \cdot kg^{-1}$)	0.26 ± 0.04	0.27 ± 0.12
MAP (mm Hg)	120 ± 23	83 ± 10[b]
Heart rate (beats/min)	194 ± 43	217 ± 48
dP/dT (mm Hg/sec)	3547 ± 843	3600 ± 890
TPRI	444 ± 137	349 ± 148[b]

All values are mean ± SD.

Abbreviations: MAP, mean aortic pressure; TPRI, total peripheral resistance index.

[a] From Boudreaux et al. (2).

[b] $P < 0.05$ vs isoflurane.

to-mean MAC for blood, atrium, and brainstem were 2.04, 2.00, and 2.84, respectively. The LD:MAC ratio of isoflurane blood concentrations for the seven animals in whom blood samples were obtained at both doses was 2.0 ± 0.4 (SD). The LD:MAC ratio of isoflurane heart concentrations for the two animals in whom paired atrial specimens were obtained was 2.1 ± 1.2. Brainstem tissue was not obtained from any animal at both MAC and LD.

Discussion

Isoflurane caused profound hemodynamic changes in healthy newborn piglets. Social development of the piglet during the age range studied probably corresponds to the first half-year of human life (2). However, the hemodynamic responsiveness of the piglet during the first 2 ½ weeks of life is fairly consistent and corresponds to the human newborn. The large reduction in peripheral resistance and blood pressure with preservation of cardiac output seen here was also observed in healthy adult humans (8). A key difference between adults and children is the heart rate response to isoflurane. Healthy adults have mild tachycardia, but infants and children (like our piglets) develop moderate-to-severe bradycardia. The imbalance between the well-developed parasympathetic nervous system and the immature sympathetic nervous system of the newborn may be responsible (9). Isoflurane blunts the baroreceptor heart rate response. Isoflurane depresses the heart rate response to sympathetic stimulation more than it depresses the

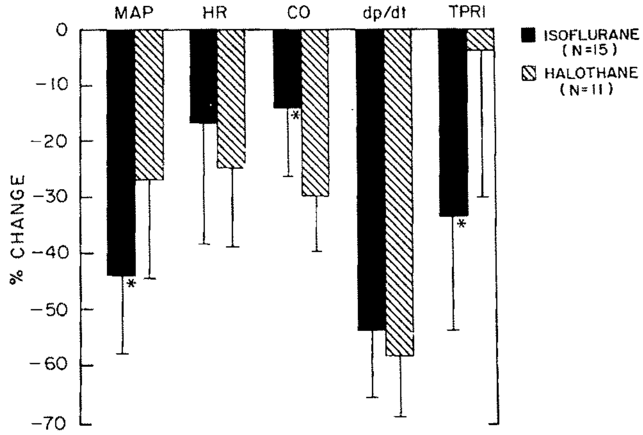

Figure 2. Hemodynamic changes from baseline in piglets given 1.3 MAC isoflurane vs 1.3 MAC halothane. *$P < 0.05$. MAP, mean aortic pressure; HR, heart rate; CO, cardiac output; dP/dT, first derivative of LV pressure with respect to time; TPRI, total peripheral resistance index.

Table 4. Isoflurane Tissue Concentrations

	MAC	Lethal Concentration
Blood (mg/100 ml)	13.4 ± 2.9 (n = 12)	27.4 ± 5.2 (n = 7)
Atrium (mg/100 g)	20.6 ± 8.1 (n = 5)	41.1 ± 10.3 (n = 7)
Brainstem (mg/100 g)	22.9 ± 13.8 (n = 3)	65.1 ± 5.2 (n = 6)

All values are mean ± SD.

response to vagal efferent cardiac nerve stimulation (10). This accentuates the parasympathetic–sympathetic imbalance and promotes bradycardia. However, when atrial pacing was used to control the heart rate, the changes in MAP, TPRI, and dP/dT/DP40 persisted, suggesting that they were affected by other primary mechanisms.

Isoflurane profoundly depressed myocardial contractility, as shown by the reduced dP/dT, a pre-ejection phase index, and reduced shortening fraction, an ejection phase index. Left ventricular peak dP/dT may be reduced if heart rate, LVEDP, or aortic diastolic pressure is decreased (7). We therefore measured LV dP/dT/DP40, since this pre-ejection phase derivative is independent of the reduction in aortic diastolic pressure that occurred during isoflurane anesthesia in these animals. Any potential effects caused by a change in heart rate were obviated by fixed atrial pacing. Under these conditions, dP/dT/DP40 decreased with isoflurane and was not improved by pacing.

Because MAP and TPRI decreased to a similar extent at 0.5 and 1.0 MAC, their quotient, cardiac output, changed very little. At 1.3 MAC, the profound reduction in MAP was only partly offset by the smaller reduction in TPRI. Although cardiac output therefore decreased, its change was not significant. At all concentrations, estimated preload (LVEDP) changes were not significant.

The LD:MAC ratio measured by others in adult rat heart and brain was 2.5–3.5 times higher than in these piglets (11). This presumably represents a difference between species and/or age.

Several differences between the isoflurane and halothane groups warrant discussion. The mean baseline values of MAP and TPRI were significantly different between the halothane and isoflurane groups. The former group tended to be younger, although not significantly so. In a previous study, we reported the relationship between each baseline variable and animal age using this animal model (2). In that study, MAP (only) was significantly correlated with age ($r = 0.7$, $P < 0.05$). This might explain the difference between the isoflurane and halothane groups in baseline MAP and its dependent variable, TPRI. To remove such bias, each animal served as its own control, and the change from baseline was calculated for each animal.

Although both halothane and isoflurane reduced blood pressure considerably, the large reduction in peripheral resistance caused by isoflurane offset the hypotension and prevented a major decrease in cardiac output. Because cardiac output was stable, isoflurane might be safer in infants than halothane. However, the major reduction in blood pressure caused by isoflurane cannot be ignored. Although regional blood flow can be adjusted by autoregulation during hypotension, the blood pressure limits of effective autoregulation are not well-defined for most regional vascular beds in the newborn infant. These profound reductions in MAP might exceed the bounds of autoregulation, causing lower blood flow to vital organs. This hypothesis could be tested by determining regional blood flows at different isoflurane concentrations. If, despite hypotension, isoflurane does not reduce regional organ perfusion of vital organs, it would have a clear advantage over halothane. The profound reduction in contractility caused by isoflurane appears to be well-tolerated in healthy newborn piglets, because they maintained a normal cardiac output without metabolic acidemia for about 2 hr while breathing 1.0–1.3 MAC isoflurane.

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Cerebrovascular and Cerebral Metabolic Effects of Physostigmine, Midazolam, and a Benzodiazepine Antagonist

William E. Hoffman, PhD, Ronald F. Albrecht, MD, David J. Miletich, PhD,
Timothy J. Hagen, PhD, and James M. Cook, PhD

HOFFMAN WE, ALBRECHT RF, MILETICH DJ, HAGEN TJ, COOK JM. Cerebrovascular and cerebral metabolic effects of physostigmine, midazolam, and a benzodiazepine antagonist. Anesth Analg 1986;65:639–44.

Physostigmine has been reported to reverse the sedation and paradoxical delirium induced by benzodiazepines. Little is known about how these drugs may interact to produce changes in cerebral metabolism and cerebral blood flow (CBF). In the present experiments, the effect of physostigmine on cerebral oxygen consumption ($CMRO_2$) and CBF as well as the ability of physostigmine to reverse the effects of midazolam and 3-carbo-t-butoxy-B-carboline (B-CCT), a benzodiazepine antagonist, was tested in rats. Physostigmine by itself produced dose-dependent increases in blood pressure, CBF, and $CMRO_2$, and it inhibited the decrease in these parameters produced by midazolam. Alone, B-CCT increased CBF and $CMRO_2$, and these changes were potentiated by physostigmine. Thus, physostigmine increases CBF and $CMRO_2$, probably by a direct effect on central cholinergic pathways. The ability of physostigmine to antagonize the metabolic effects of midazolam and to potentiate the stimulation produced by B-CCT suggests an additive effect of the two neurotransmitter systems rather than a direct interaction at the central receptor sites.

Key Words: HYPNOTICS—benzodiazepines. BRAIN—blood flow. ANTAGONISTS, MISCELLANEOUS—physostigmine.

Benzodiazepines, including diazepam and midazolam, are often used for sedation before anesthesia. Although relatively few side effects have been reported with benzodiazepines and phenothiazines, respiratory depression may be apparent and coma may even occur (1–3). In addition to sedation, benzodiazepines can also produce toxicity and delirium (4,5). The ability of benzodiazepines to produce either sedation or delirium may be due to an action at central benzodiazepine receptors. Behavioral depression and stimulation can be induced in animal models with benzodiazepines and their receptor antagonists, B-carbolines, respectively (6–8). Benzodiazepines and B-carbolines have also been shown to produce cerebral metabolic depression and stimulation, respectively, consistent with their behavioral effects (9,10). The clinical side effects of benzodiazepines, including respiratory depression, coma, and delirium have been reversed with physostigmine (4,5,11–13). However, the mechanism of this action is unclear. Midazolam has been shown to have anticholinergic activity in the mammalian CNS (14). Another possibility is that physostigmine may interact directly or indirectly with a benzodiazepine receptor to antagonize both the depressive and stimulatory effects produced by benzodiazepine drugs (4,5,13). In this regard, it has been suggested that physostigmine may directly antagonize the effect of benzodiazepines at the benzodiazepine-gamma aminobutyric acid receptor-chloride ionophore complex (15). In order to test these hypotheses, the cerebrovascular and cerebral metabolic effects of midazolam and 3-carbo-*t*-butoxy-B-carboline (B-CCT) were tested alone and with physostigmine treatment.

Methods

Surgical Preparation

One hundred twenty-two 6-month-old male Sprague–Dawley rats were used in these experiments. Rats were anesthetized with halothane in a bell jar, tracheotomized, and ventilated with 1% inspired concentration of halothane in O_2 using a Harvard small animal respirator. Body temperature was maintained at 37°C, and arterial PCO_2 was maintained between

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Address correspondence to Dr. Hoffman, Anesthesiology Department, Michael Reese Hospital, Chicago, IL 60616.

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Table 1. Cardiovascular and Blood Gas Changes Produced by Physostigmine, Midazolam, and B-CCT

	n	Blood pressure (mm Hg)	Heart rate (min^{-1})	Pa_{CO_2} (mm Hg)	Pa_{O_2} (mm Hg)	Ca-v_{O_2} (ml O_2/100 ml)	pH
Physostigmine dose[a]							
0	9	151 ± 3	434 ± 8	36.0 ± 0.8	145 ± 7	5.5 ± 0.3	7.43 ± 0.02
0.1	7	145 ± 1	425 ± 2	37.3 ± 0.3	143 ± 1	5.1 ± 0.1	7.39 ± 0.01
0.4	8	178 ± 2[b]	440 ± 2	33.4 ± 0.4	132 ± 2	4.4 ± 0.2	7.38 ± 0.01
1.0	7	190 ± 2[b]	432 ± 6	36.4 ± 0.8	112 ± 5[b]	3.4 ± 0.2[b]	7.31 ± 0.01[b]
Midazolam dose[a]							
0	9	155 ± 4	445 ± 7	36.1 ± 0.7	139 ± 7	3.9 ± 0.2	7.42 ± 0.01
0.5	7	140 ± 2[b]	411 ± 8[b]	35.8 ± 0.3	145 ± 2	5.8 ± 0.2[b]	7.43 ± 0.01
5.0	9	127 ± 3[b]	394 ± 3[b]	35.8 ± 0.2	143 ± 3	6.6 ± 0.1[b]	7.41 ± 0.01
Midazolam dose with physostigmine (0.4 mg/kg)[a]							
0.5	9	149 ± 2	438 ± 4	36.5 ± 0.2	158 ± 2	5.8 ± 0.1[b]	7.37 ± 0.01
5.0	12	153 ± 1	430 ± 4	36.2 ± 0.3	144 ± 2	5.7 ± 0.1[b]	7.41 ± 0.01
B-CCT dose[c]							
0	9	156 ± 3	447 ± 7	36.3 ± 0.8	143 ± 6	4.1 ± 0.2	7.43 ± 0.01
1.0	9	151 ± 1	420 ± 6	36.6 ± 0.2	132 ± 4	4.4 ± 0.1	7.44 ± 0.01
10.0	9	155 ± 1	423 ± 3	39.4 ± 0.3	156 ± 3	4.4 ± 0.1	7.41 ± 0.01
B-CCT dose with physostigmine (0.4 mg/kg)[a,c]							
1.0	9	161 ± 1[b]	430 ± 4	38.1 ± 0.4	142 ± 2	4.3 ± 0.2	7.40 ± 0.01
10.0	9	167 ± 1[b]	430 ± 5	36.8 ± 0.3	136 ± 3	4.6 ± 0.1	7.38 ± 0.01

All doses in mg/kg.

[a] Intraperitoneal doses for physostigmine and midazolam.

[b] $P < 0.05$ compared to zero dose control.

[c] Intravenous dose for B-CCT.

35 and 40 mm Hg by adjusting ventilation. Bilateral cutdowns were performed for cannulation of both femoral arteries and both femoral veins with Clay-Adams Intramedic polyethylene catheters filled with heparinized normal saline solution. These catheters were used for continuous heart rate and pressure monitoring, blood withdrawal, and drug administration. The left ventricle was catheterized via the right common carotid artery for microsphere injections. Pressure tracings were monitored to ensure proper catheter placement. A Hewlett-Packard pressure transducer and chart recorder was used in all cases. The skull was exposed, a small hole drilled into the sagittal sinus and a catheter inserted for withdrawal of sagittal sinus blood samples.

After completion of surgery, halothane was discontinued and the animal was given 50% N_2O and 50% O_2 for a 45-min equilibration period. Muscle relaxation was achieved with 1 mg/kg intravenous *d*-tubocurarine.

Drug Administration

Animals were assigned to one of several treatment schedules. In part one, rats were selected to determine the effects on cerebral blood flow and metabolism of intraperitoneally injected physostigmine in varying doses. Doses were 0, 0.1, 0.4, and 1.0 mg/kg. Microsphere injections and blood gas measurements were made 10 min after the injection of physostigmine.

In part two, rats were subjected to either intraperitoneal bolus injection of 0.5 or 5.0 mg/kg midazolam followed 5 min later by an intraperitoneal injection of saline, or an intraperitoneal bolus injection of 0.5 or 5.0 mg/kg midazolam followed 5 min later by an intraperitoneal injection of 0.4 mg/kg physostigmine. A microsphere test was performed 10 min after the physostigmine or vehicle injection. Nine rats serving as controls received an intraperitoneal saline injection followed 5 min later by a second intraperitoneal saline injection. Microsphere tests were performed in these rats 10 min after the second injection.

In part three, rats received either an intravenous bolus injection of 1.0 or 10.0 mg/kg B-CCT followed immediately by an intraperitoneal injection of saline or an intravenous bolus injection of 1.0 or 10.0 mg/kg B-CCT followed immediately by an intraperitoneal injection of 0.4 mg/kg physostigmine. Testing with microspheres was performed 10 min after these procedures. Nine rats serving as controls received intravenous and intraperitoneal saline vehicle injections 10 min before the microsphere test.

Microspheres

Microsphere injections were performed using 15 μm microspheres labelled with cobalt-57 (New England Nuclear). Stock solutions containing 500,000 microspheres/ml were suspended in isotonic saline with 0.1% Tween-80. Ventricular pressure tracings were

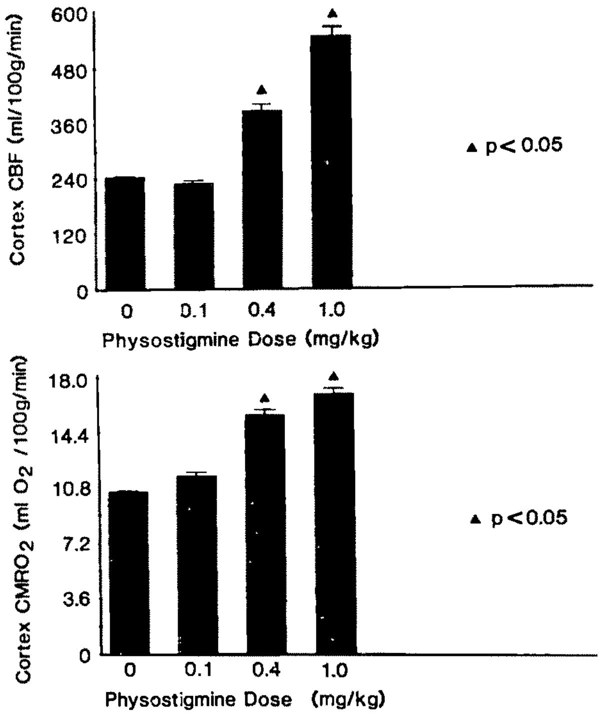

Figure 1. Effect of physostigmine on CBF and $CMRO_2$. Number of animals in each group shown in Table 1. Significance values indicate difference from zero dose control levels.

monitored before each microsphere injection. Microspheres were vortexed for 1 min, then 0.2 ml were withdrawn (100,000 microspheres) and injected into the left ventricle via the ventricular catheter (dead space = 0.06 ml) and flushed in with 0.2 ml saline. Starting immediately before the microsphere test and continuing 45 sec after the end of each injection, blood was withdrawn from a femoral artery at a rate of 0.4 ml/min using a Harvard infusion–withdrawal pump. Arterial blood gas measurements were made at the end of the microsphere injection procedure. Arterial and sagittal sinus blood samples were also taken after each microsphere test for measurement of cerebral arterial-venous O_2 content ($Ca\text{-}vO_2$). Blood gas tensions and pH were measured with an IL 1303 blood gas analyzer and oxygen content was measured using an IL 282 cooximeter. Mean arterial blood pressure was measured continuously throughout the microsphere tests from the second femoral artery to ensure blood pressure did not change appreciably. Heart rate was measured before each microsphere injection. At the end of the microsphere test the rat was killed and the brain was removed and sectioned into left and right cortical and subcortical samples and weighed. The microsphere activity in brain and blood samples was analyzed using a Nuclear Chicago 1035 Gamma Counter and a Nuclear Data 600 multichannel analyzer. Cerebral blood flow was determined in each sample using the methods of Heymann et al. (16), but only cortical cerebral blood flow (CBF) is reported here. Cerebral oxygen consumption ($CMRO_2$) was calculated as the product of cortical CBF, corrected for brain weight, and $Ca\text{-}vO_2$.

Drug and Reagents

Midazolam maleate (RO 21-3981/1, Hoffman-La-Roche, Inc., Nutley, NJ) and physostigmine were dissolved in normal saline for intraperitoneal injection. B-CCT was suspended in saline by sonication at the time of injection.

Statistical Methods

All data are reported as mean ± SEM. Statistical tests included a one-way analysis of variance to analyze physostigmine treatment effects alone and a two-way ANOVA to compare midazolam and B-CCT treatment effects with and without physostigmine. Unpaired t-tests were used to compare individual group differences using a Bonferroni correction.

Results

Cardiovascular and blood gas changes produced by physostigmine are shown in Table 1. Physostigmine produced dose-dependent increases in blood pressure which were significant at 0.4 mg/kg. At the highest physostigmine dose, 1 mg/kg, blood pressure was increased while PaO_2, $Ca\text{-}vO_2$, and pH were decreased. Cortical CBF and $CMRO_2$, shown in Figure 1, both increased after physostigmine administration, and these changes were significant as determined by ANOVA: CBF, $F = 14.67$, $P < 0.001$; $CMRO_2$, $F = 20.77$, $P < 0.001$.

Midazolam given alone produced decreases in blood pressure and heart rate and increases in $Ca\text{-}vO_2$ (Table 1). These changes were reversed by physostigmine. Cortical CBF and $CMRO_2$, shown in Figure 2, decreased after midazolam treatment: CBF, $F = 13.47$, $P < 0.001$; $CMRO_2$, $F = 15.22$, $P < 0.001$. Physostigmine in combination with midazolam increased CBF and $CMRO_2$ when compared with midazolam alone: CBF, $F = 21.12$, $P < 0.001$; $CMRO_2$, $F = 24.11$, $P < 0.001$.

No significant change in blood pressure, heart rate, or blood gases was produced by B-CCT alone (Table 1). Physostigmine (0.4 mg/kg) given with B-CCT increased blood pressure, but had no effect on heart rate. When given alone, B-CCT did increase CBF and $CMRO_2$ (Fig. 3): CBF, $F = 7.66$; $CMRO_2$, $F = 9.64$,

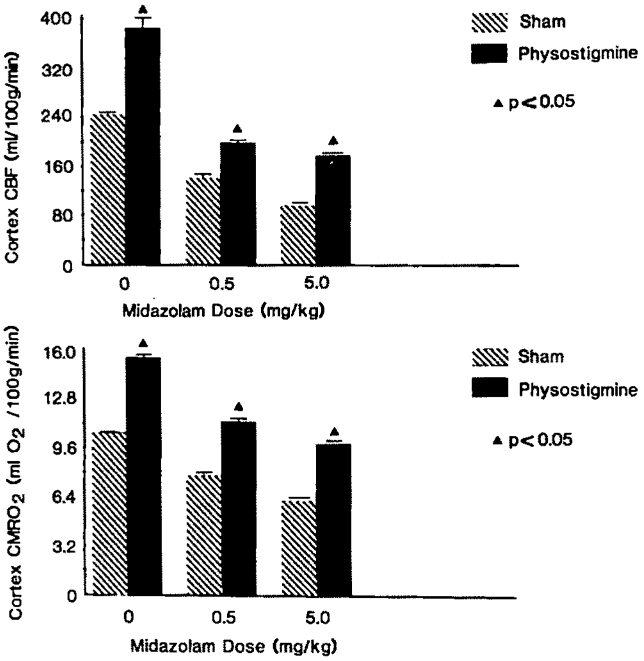

Figure 2. Effect of midazolam on CBF and $CMRO_2$ with and without physostigmine (0.4 mg/kg). Significance values indicate difference between physostigmine and sham-treated rats at each midazolam dose.

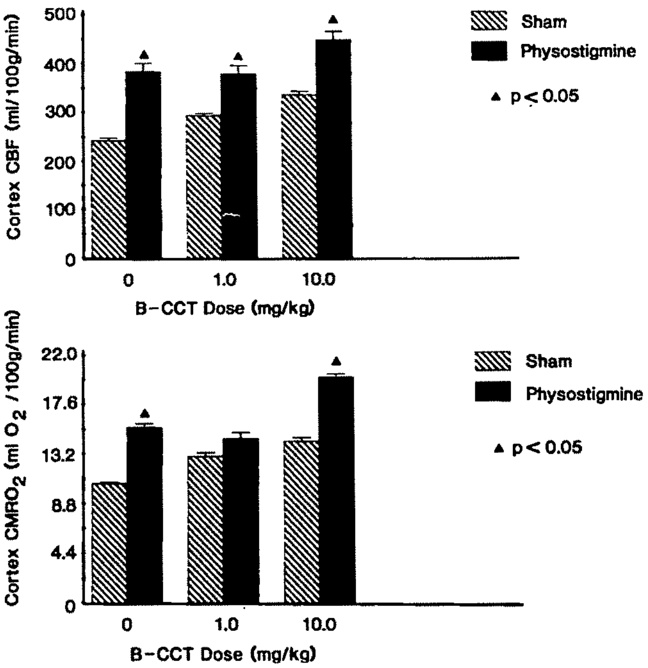

Figure 3. Effect of B-CCT on CBF and $CMRO_2$ with and without physostigmine. Significance values indicate difference between physostigmine and sham-treated rats at each B-CCT dose.

$P < 0.01$. These increases in cortical CBF and $CMRO_2$ were potentiated by physostigmine in combination with B-CCT: CBF, $F = 8.00$; $CMRO_2$, $F = 10.27$, $P < 0.01$.

Discussion

It was hypothesized in these studies that stimulation of central receptors with physostigmine may directly interact with and reverse both CBF and $CMRO_2$ depression and stimulation produced by central benzodiazepine receptor activation. This hypothesis was based on clinical studies that showed that physostigmine will reverse both the sedation and the delirium that may occur following benzodiazepine administration (3–5), and upon binding studies in vitro that indicated that physostigmine is a competitive inhibitor at benzodiazepine receptors in rat cortex (15). The results of this study show that physostigmine by itself increases CBF and $CMRO_2$, and will antagonize the decrease in CBF and $CMRO_2$ produced by midazolam. However, physostigmine did not significantly decrease the cerebrovascular and metabolic stimulation produced by the benzodiazepine antagonist, B-CCT, but potentiated these effects. This would suggest that physostigmine does not inhibit benzodiazepine receptor stimulation by a direct antagonistic effect but by an indirect stimulatory effect which is additive with benzodiazepines or their antagonists.

High-affinity, stereospecific benzodiazepine binding sites have been identified in the mammalian CNS that are physically as well as functionally linked to the GABA receptor and the chloride ionophore. Gamma aminobutyric acid acts at the benzodiazepine-GABA receptor-chloride ionophore by directly increasing conductance of the chloride ionophore and inhibiting the activity of the neuron (7). Benzodiazepines act at this complex by modulating the activity of the GABA receptor. Benzodiazepines such as diazepam and midazolam are used clinically as preanesthetic sedative agents. They have also been shown to decrease CBF and $CMRO_2$ by themselves, and to potentiate these effects in combination with other agents such as alcohol (10,17,18). B-Carbolines have been shown to be potent direct antagonists of central benzodiazepine receptor binding, as well as having intrinsic actions of their own generally opposite to those of benzodiazepines (6,10). B-CCT has previously been shown to increase CBF and $CMRO_2$ and to inhibit the cerebral metabolic depression produced by midazolam, or midazolam in combination with alcohol (17). A dose-related increase in CBF and $CMRO_2$ was also seen here with B-CCT. However, this increase was not significantly inhibited by physostigmine treatment, and the cerebral metabolic stimulation produced by physostigmine was additive with that of B-CCT. This finding suggests that although physostigmine effectively inhibits the decrease in CBF and CMRo$_2$ produced by midazolam, it does so not by a direct inhibition of binding at the benzodiazepine receptor, but by separate cerebral metabolic and cerebrovascular effects, which are additive with those of midazolam and B-CCT.

Studies suggest that central cholinergic mechanisms may be important in the control of CBF and brain metabolism. Scremin et al. (19) reported that desynchronization of EEG in rats produced increases in CBF that could be blocked by local application of atropine and exaggerated by eserine, a cholinergic agonist. Other reports agree that cholinergic drugs will increase CBF (20). It has been suggested that the central vasodilating action of physostigmine may protect the brain from hypoxic injury (21). However, the protection afforded by physostigmine in other hypoxic models is reported to be modest at best (22). Part of the reason may be that physostigmine increases CMRo$_2$ with CBF, moderating any potential benefit produced by increased brain perfusion. Several reports indicate that physostigmine treatment increases local cerebral glucose metabolism (23–25). However, certain anesthetic drugs such as ketamine and morphine may inhibit the cardiovascular and cerebral metabolic effect of physostigmine (26,27). Results here also show that CBF and CMRo$_2$ both increase after physostigmine injection. Although there is no clear evidence of the mechanism by which physostigmine increases CBF and CMRo$_2$, apparently central cholinergic receptors are involved (25). Other neurotransmitters may also be involved, including serotonin, norepinephrine, GABA, and benzodiazepine receptors (28–30). Although results reported here and elsewhere suggest that physostigmine may antagonize the sedation and cerebral metabolic depression produced by benzodiazepines (31), the effect appears to be due to physostigmine's direct effects on cerebral metabolism, rather than to a competitive inhibitory effect on benzodiazepine receptors as suggested previously (15).

Previously physostigmine has been reported to produce hypertensive effects by central cholinergic receptor stimulation; the effects are mediated by increases in peripheral sympathetic activity (32). Increases in blood pressure were also observed here after physostigmine administration. It is unlikely that the hypertension significantly altered CBF at the two lower doses of physostigmine because the blood pressure did not increase beyond the normal range of cerebral autoregulation in the rat (33). Cerebral blood flow changes at these doses were also consistent with changes in CMRo$_2$, suggesting that the increases in cerebral perfusion were due to increases in cerebral metabolic rate and normal coupling between blood flow and metabolism. With 1.0 mg/kg physostigmine, blood pressure approached the upper limit of cerebral autoregulation. In addition, a slight but significant acidosis developed. Both of these factors may increase CBF above normal metabolic requirements (33,34). This appeared to be the case, because CBF increased more than CMRo$_2$ at the 1.0 mg/kg physostigmine dose, and cerebral oxygen extraction decreased significantly. Neither of the two lower doses of physostigmine produced the same degree of hypertension, acidosis, or decrease in cerebral oxygen extraction seen with 1.0 mg/kg physostigmine, which suggests that CBF was not altered separately from CMRo$_2$ with the 0.1 and 0.4 mg/kg physostigmine treatments, and that normal coupling between blood flow and metabolism was present.

In conclusion, data here indicate that physostigmine increases CBF and CMRo$_2$, as reported previously. The increases in CBF are linked primarily to increases in CMRo$_2$ and a normal coupling between blood flow and metabolism. Midazolam decreased CBF and CMRo$_2$ in a dose-related manner, and this decrease was antagonized by physostigmine. B-CCT, a benzodiazepine antagonist, increased CBF and CMRo$_2$, but this change was potentiated by physostigmine. These results suggest that physostigmine antagonizes the central action of benzodiazepines by a central stimulatory action, and not by the direct competitive effect at the benzodiazepine receptor that had been suggested previously. If physostigmine produces stimulation by an action at the central benzodiazepine–GABA receptor chloride ionophore complex, this action is probably independent of the benzodiazepine receptor.

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Gas Exchange during Controlled Ventilation in Children with Normal and Abnormal Pulmonary Circulation:

A Study Using the Single Breath Test for Carbon Dioxide

Roger Fletcher, MD, FFARCS, Lisbet Niklason, and Björn Drefeldt

FLETCHER R, NIKLASSON L, DREFELDT B. Gas exchange during controlled ventilation in children with normal and abnormal pulmonary circulation: a study using the single breath test for carbon dioxide. Anesth Analg 1986;65:645–52.

Carbon dioxide single breath tests (SBT-CO_2) were obtained during anesthesia and controlled ventilation in 42 children about to undergo thoracic surgery. The tests were obtained with a computerized system based on the Servo ventilator. The system made on-line corrections for compressed volume, apparatus deadspace, and rebreathing. Children with normal pulmonary circulation had excellent gas exchange with high Pa_{O_2} *values, a mean alveolar deadspace fraction* (V_D*alv/*V_T*alv) of 0.10, and a gently sloping phase III of SBT-CO_2. Children with pulmonary hyperperfusion (left to right shunting) due to an atrial septal defect or a ventrical septal defect had significantly lower* Pa_{O_2} *values, steeper phase III slopes, and a greater spead of values for* V_D*alv/*V_T*alv. Children with pulmonary hypoperfusion due to pulmonary stenosis in combination with intracardiac right to left shunting had extremely low* Pa_{O_2} *values, and "adult" values for* V_D*alv/*V_T*alv. They required increased ventilation to maintain* CO_2 *homeostasis. In the pooled material, the airway deadspace was strongly correlated to height, weight, and age. The airway deadspace was unaffected when tidal volume was increased by 37%, and ventilatory frequency simultaneously reduced by 30%, a maneuver that left alveolar ventilation unchanged. This is probably because an end-inspiratory pause was used; when frequency is reduced the length of the end-inspiratory pause increases, allowing proximal diffusion of the alveolar/fresh gas interface.*

Key Words: VENTILATION—pediatric. ANESTHESIA—pediatric.

Many children presenting for cardiovascular surgery have lesions that affect perfusion of the lung. A patent ductus arteriosus (PDA) will give rise to a small to moderate degree of pulmonary hyperfusion, i.e., left to right (L–R) shunt. Greater degrees of L–R shunt can be seen with an atrial septal defect (ASD) or a ventricular septal defect (VSD), the latter often giving rise to pulmonary hypertension. In these, arterial oxygenation is only moderately reduced.

When pulmonary stenosis (PS) occurs as an isolated defect, the circulation is normal or hypokinetic, but PS combined with an intracardiac right to left (R–L) shunt gives rise to pulmonary hypoperfusion with hypoxemia. In transposition of the great arteries (TGA), both the pulmonary and systemic circulations may be hyperkinetic, but the large R–L shunt may give rise to an apparent alveolar deadspace, resembling genuine hypoperfusion.

It has been previously argued that the single breath test for CO_2 (SBT–CO_2) (1,2,3) is a useful tool for studying gas exchange. This plot of expired CO_2 concentration or fraction against expired volume (Fig. 1) allows measurement of the airway deadspace ($V_D$aw), which is defined as extending from the airway opening down to the interface between inspired and alveolar gas (3). During mechanical ventilation it is convenient to define the airway opening as the apparatus end of the endotracheal tube. Combined with knowledge of arterial P_{CO_2}, SBT-CO_2 allows calculation of the physiologic deadspace ($V_D$phys) and the alveolar deadspace ($V_D$alv) (from $V_D\text{alv} = V_D\text{phys} - V_D\text{aw}$). The arterial end-tidal P_{CO_2} gradient ($Pa_{CO_2} - P_{ET_{CO_2}}$), the alveolar deadspace fraction $V_D$alv/$V_T$alv, (where $V_T$alv = tidal volume, $V_T - V_D$aw), and the slope of phase III of SBT-CO_2 are of particular interest in studies of patients with abnormal lung perfusion. Phase III, representing alveolar gas, has also, perhaps somewhat misleadingly, been called the alveolar plateau.

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Address correspondence to Dr. Fletcher, Department of Anesthesiology, University Hospital, S-221 85 Lund, Sweden.

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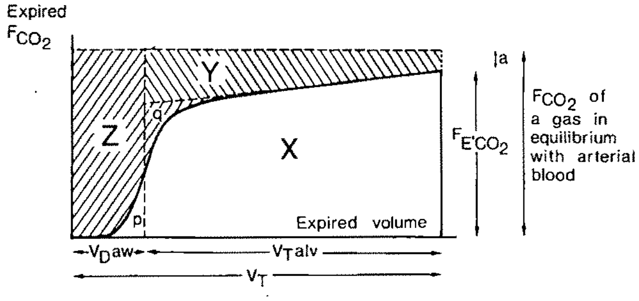

Figure 1. CO_2 single breath test, i.e., the plot of expired F_{CO_2} against expired volume. The upper horizontal line represents the F_{CO_2} of a gas in equilibrium with the arterial blood. Triangles *p* and *q* are of equal area. Area *X* represents the volume of CO_2 eliminated in the breath; areas Z and Y represent failure to eliminate CO_2 due to the airway and alveolar deadspaces, respectively.

$V_D$alv/$V_T$alv represents the degree to which alveolar ventilation ($\dot{V}$) and perfusion ($\dot{Q}$) fail to match each other. $\dot{V}/\dot{Q}$ mismatching can be regional, as in pulmonary embolism, and also global, as in asthma, chronic bronchitis, and emphysema. In pulmonary embolism (2,4) an almost horizontal phase III is the rule; in obstructive airways disease, phase III has a slope, which is proportional to the alveolar deadspace fraction and to the lung's mechanical properties such as the expiratory time constant (2,5). This paper describes SBT-CO_2 and some of the above variables during undisturbed anesthesia.

Methods

The patients were 42 infants and children about to undergo elective thoracic surgery. Details of their ages, diagnoses, and gas exchange are given in Table 1. Children whose height or weight differed from their predicted values by more than two standard deviations (6) are marked with a footnote. In order to facilitate analysis of the results, the children were divided into four groups: ten controls, with normal pulmonary perfusion; 16 children with pulmonary hyperperfusion (R–L shunting) due to ASD and/or VSD; six with hypoperfusion (R–L shunting); and ten unclassifiable because of the mixed nature of their lesions. These divisions were based on the results of preoperative investigations, including x-ray, cardiac catheterization, ultrasound, in addition to the Pa_{O_2} values obtained during anesthesia.

Anesthesia was provided with N_2O, 50% in O_2; fentanyl and droperidol (cardiac surgery); or with N_2O, fentanyl, and halothane, 0.5% (repair of coarctation, closure of PDA via thoracotomy). Long-acting muscle relaxants were used sparingly and were not given close to the time when measurements were made.

The ventilator used was a Servo 900C; frequencies were 25–35 breaths/min depending on age of the patient. Constant flow inflations, 25% of cycle, 10% end-inspiratory pause (EIP), and zero positive end-expiratory pressure were used throughout. No humidifier was in use during data collection. Air-tightness in the tubings was tested by using the "inspiratory pause hold" on the ventilator for a few seconds, and observing airway pressure. At steady state and with the patients in the supine position during undisturbed anesthesia, three SBT-CO_2 tracings were recorded and 2 ml of arterial blood slowly withdrawn for immediate analysis (ABL2; Radiometer, Copenhagen). The blood gas analyzer's own internal calibration did not vary by more than 0.7 mm Hg during periods of data collection.

Arterial P_{CO_2} was temperature corrected. In 14 children esophageal temperature was obtained; in the remainder, only rectal temperature was available. Their true central temperature was obtained by the following formula: Central temperature, °C = 0.594 × rectal temperature + 15.0; residual standard deviation (RSD) = 0.25; r = 0.89. This equation was obtained from 28 observations in the 14 children in whom both rectal and esophageal temperature had been recorded after towelling and draping, but before sternotomy. The children were in a state of relative thermal stability at the time of measurement, after the initial heat loss associated with induction, arterial and venous cannulation, and urinary catheterization.

SBT-CO_2 was recorded using an on-line computer system (7). The system uses, in addition to the ventilator, a CO_2 analyzer 930 coupled to a Facit DTC computer that presents and stores the SBT-CO_2 tracing. When a value for Pa_{CO_2} is given to the computer, the "invasive" (8) variables $V_D$phys and $V_D$alv are calculated. Airway deadspace is measured as the point of inflexion of phase II, i.e., the point of maximum rate of rise of F_{CO_2}. The values for $V_D$aw obtained by this method are generally close to those obtained by the equal area method (Fig. 1); however, the latter is a more difficult task for the computer. In some cases a visual "best fit" was preferred. This is simple to perform in the absence of airway disease—it is the expired volume at F_{CO_2} = 0.5 × initial phase III F_{CO_2}. "Best fit" was used in children in whom serial measurements were also made at different stages of surgery (9,10), where SBT-CO_2 may change shape. The coefficient of variation of the three samples with the chosen method was 3.8 ± 1.4% (range 2–6%). The coefficient of variation of $V_D$phys/V_T was 3.9 ± 3.0% (range 0.0–7.6). $V_D$alv was obtained from the mean $V_D$phys from 3 samples − mean $V_D$aw.

Siemens–Elema pediatric tubings, Y-piece, and CO_2 cuvette were used. The rebreathing volume of the

Table 1. Diagnoses, Ages, and Gas Exchange Variables

	Age (yr)	V_T (ml)	V_D aw (ml)	$\frac{V_D \text{ alv}}{V_T \text{ alv}}$	$\frac{V_D \text{ phys}}{V_T}$	PaO_2 (mm Hg)
Children with normal pulmonary circulation						
1.[a] PS[b]	1.9	97	21	0.12	0.31	265
2. AS	4.8	159	33	0.14	0.32	268
3. PS[c]	5.8	132	—	0.07	—	256
4. PS	3.5	121	16	0.12	0.23	207
5. AS, PS[b]	0.9	102	13	0.08	0.20	216
6. PDA, normal chest x-ray	8.9	210	24	0.09	0.20	307
7. PDA, normal chest x-ray	6.8	171	25	0.06	0.20	269
8. PDA, normal chest x-ray	5.8	152	32	0.12	0.30	292
9. Coarctation of aorta[b]	1.5	95	16	0.10	0.25	175
10. PDA, normal chest x-ray	6.5	177	23	0.06	0.18	196
Mean	4.6	143	23	0.10	0.24	245
SD	2.6	41	7	0.03	0.05	44
Children with increased pulmonary circulation						
11. VSD, shunt 3:1 cardiomegaly, widened pulmonary vessels[b]	3.9	122	28	0.09	0.30	193
12. ASD, shunt 2.4:1, cardiomegaly, widened pulmonary vessels	6.3	157	36	0.11	0.32	200
13. ASD, VSD, shunt 3:1 cardiomegaly, widened pulmonary vessels[b]	0.8	69	11	0.17	0.30	154
14. ASD cardiomegaly widened pulmonary vessels	5.2	152	18	0.15	0.25	205
15. ASD, shunt 3:1, cardiomegaly widened pulmonary vessels	5.3	147	31	0.10	0.29	127
16. VSD, PDA shunt 2.8:1, cardiomegaly widened pulmonary vessels	1.2	87	14	0.11	0.25	249
17. ASD, shunt 2.3:1, widened pulmonary vessels	8.4	265	36	0.26	0.36	174
18. VSD, pulmonary hypertension	0.8	92	11	0.13	0.23	233
19. ASD, shunt 2:1	11	200	39	0.20	0.36	173
20. ASD	7.3	163	40	0.07	0.30	245
21. PDA, widened pulmonary vessels	4.6	162	21	0.06	0.18	246
22. PDA, widened pulmonary vessels	1.4	95	13	0.05	0.18	197
23. PDA, widened pulmonary vessels	6.1	136	16	0.12	0.22	236
24. PDA (large) recent cardiac failure[b]	0.5	46	9	0.15	0.32	148
25. PDA widened pulmonary vessels[b]	1.2	78	10	0.07	0.19	253
26. PDA, 2:1 shunt	1.1	114	13	0.21	0.30	97
Mean	4.1	130	22	0.13	0.28	197
SD	3.2	53	11	0.06	0.06	46
Children with pulmonary hypoperfusion						
27. Single ventricle, PS	4.4	122	16	0.29	0.39	56
28. Fallot's tetralogy[b]	3.2	80	14	0.17	0.32	64
29. PS, ASD, R–L shunt	2.4	100	14	0.15	0.27	75
30. Transposition, PS, prostaglandin therapy	0.1	22	5	0.43	0.56	51
31. PS, VSD, double outlet RV[b]	1.5	80	11	0.44	0.52	43
32. Transposition	5.2	155	26	0.32	0.43	54
Mean	2.8	93	14	0.30	0.41	58
SD	1.9	45	7	0.12	0.11	11
Children with unclassifiable lesions						
33. VSD, transposition[b]	0.6	80	15	0.28	0.42	46
34. AV commune, pulmonary hypertension	0.7	64	6	0.12	0.20	92
35. "Acyanotic Fallot"	0.7	64	9	0.14	0.26	126
36. Anomalous pulmonary venous drainage	0.3	49	12	0.22	0.41	54
37. "Acyanotic Fallot"	1.5	109	14	0.23	0.33	232
38. ASD, VSD, pulmonary hypertension	0.6	49	7	0.25	0.36	68
39. Fallot	2.7	102	14	0.17	0.28	79
40. AV commune, PDA[b]	1.4	63	10	0.23	0.35	58
41. "Acyanotic Fallot"	4.3	146	21	0.08	0.21	166
42. VSD, ductus arteriosus aneurysm	0.3	58	9	0.32	0.43	66
Mean	1.3	78	12	0.20	0.33	99
SD	1.3	31	4	0.08	0.08	60

See text for abbreviations.

[a] Numbers in this column are patient numbers.

[b] Differs from expected value for height or weight by more than two SDs.

[c] Approximate value for $V_T \cdot V_D$aw and $V_D$phys could not be calculated with certainty because of artifact in phase I. Value for $V_D$alv/$V_T$alv, however, is accurate.

pediatric cuvette and Y-piece (11) was estimated with the use of isotopes to be equivalent to about 3 ml end-expiratory gas. Expired gas that passes through the CO_2 transducer and is then rebreathed is not registered during inspiration, hence the need for the correction of the tidal elimination of CO_2 performed "on-line". This is equivalent to correcting for a raised FI_{CO_2} in the deadspace equation. Compressed gas volume and apparatus deadspace were subtracted from the expired volume "on-line," and loss of water content in the connector tubing (influencing FE_{CO_2}) was also corrected for. The system was calibrated daily with signals for airway flow, pressure, and CO_2 in a mixture of equal parts N_2O and O_2. The CO_2-containing gas was checked by tonometry against the blood gas analyzer on several occasions; the largest difference found between two successive tests was 1.0 mm Hg.

The ability of the system to measure mean expired FCO_2 (FE_{CO_2}) was tested by ventilating a CO_2-producing lung model, which gave a realistic SBT-CO_2 at tidal volumes down to 25 ml and EIP pressures of 5–25 cm H_2O. The model consisted of a 0.5-L bag ventilated via an airway deadspace and a small-bore resistance to slow down emptying of the bag. CO_2 was supplied to the bag at a constant rate. (At tidal volumes above 300 ml, adult tubings and a rebreathing volume of 24 ml (11) were used.) Tidal CO_2 production and tidal volume (VT) (from which FE_{CO_2} was calculated) were noted while the expired gas from the ventilator was collected in a Douglas bag. The CO_2 concentration of the Douglas bag (FE_{CO_2}) was then analyzed by passage of the contents through the CO_2 cuvette, $ETCO_2$ being read off (2) from the on-line system.

In a different test, in order to demonstrate the performance of the CO_2 analyzer itself, the CO_2 cuvette was flushed by the ventilator at tidal volumes of 500 ml–25 ml. During the ventilator's expiratory period, the same volume of a test gas of known CO_2 concentration was passed through the cuvette, mimicking a patient's expiration; the PET_{CO_2} obtained was read.

Figure 2 shows the results of these experiments. The open circles show the ratio FE_{CO_2} (on-line): FE_{CO_2} (Douglas bag). The solid circles show the results obtained by flushing the CO_2 cuvette with the test gas. The results are expressed as: "obtained FET_{CO_2}/FET_{CO_2} at 500 ml tidal volume." Because the distribution of points for the two experiments is so similar, we believe that the inaccuracy seen at small tidal volumes is almost totally due to the performance of the CO_2 analyzer. The probable explanation is that at low tidal volumes the cuvette is not totally cleared of CO_2 during inspiration, at the end of which a new zero calibration is made. The CO_2 signal is logarithmic and is not linearized until after the new zero is registered. Because of this the effect of the zero error is grossly out of proportion to the number of CO_2 molecules present, and does not imply that the 3 ml rebreathing correction is significantly wrong. The results presented below have been corrected according to the solid line in Figure 2. Statistical comparisons were performed with Mann–Whitney's U-test, the paired *t*-test, and Fisher's exact test.

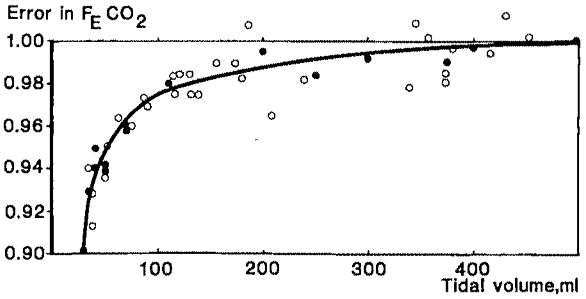

Figure 2. Results from the two validation experiments. Tidal volume is on the *x*-axis. For the first experiment (*open circles*) the *y*-axis represents FE_{CO_2} on-line system/FE_{CO_2} Douglas bag. For the second experiment (*solid circles*) the *y*-axis is FET_{CO_2}/FET_{CO_2} at 500 ml tidal volume.

Results

Figure 3 shows typical computer printouts from children representative of the three major groups. For the 31 children whose height and weight were within two standard deviations (SD) of predicted values, the regression equations for V_Daw against these two variables were the following: V_Daw (ml) = −14.4 + 35.45 × height (m) ($r = 0.84$, $P < 0.0001$) and V_Daw (ml) = 2.2 + 1.17 × weight (kg) ($r = 0.81$, $P < 0.0001$). Regressions using all children were very similar. Airway deadspace was also strongly correlated to age. Figure 4 shows the distribution for the entire material (except patient 3). Children whose length or weight deviated by more than two SD are marked. The regression for all children (Fig. 4) is V_Daw (ml) = 8.7 + 2.94 × age (yr) ($r = 0.86$, $P < 0.0001$). For the 31 normal children, V_Daw (ml) = 8.2 + 3.00 × age (yr) ($r = 0.86$, $P < 0.0001$). There were no significant differences in the V_Daw/age and V_Daw/height relationships between children anesthetized with 0.5% halothane in N_2O/O_2 ($n = 16$) and those given fentanyl, droperidol, and N_2O/O_2 ($n = 26$). The numbers are too small to permit analysis of the effect of pulmonary hypo- and hyperperfusion on V_Daw. When the ventilator setting was changed by reducing *f* by 30% and increasing VT by 37% mean V_Daw did not change (mean increase 0.9 ml, $P = 0.12$). Mean CO_2

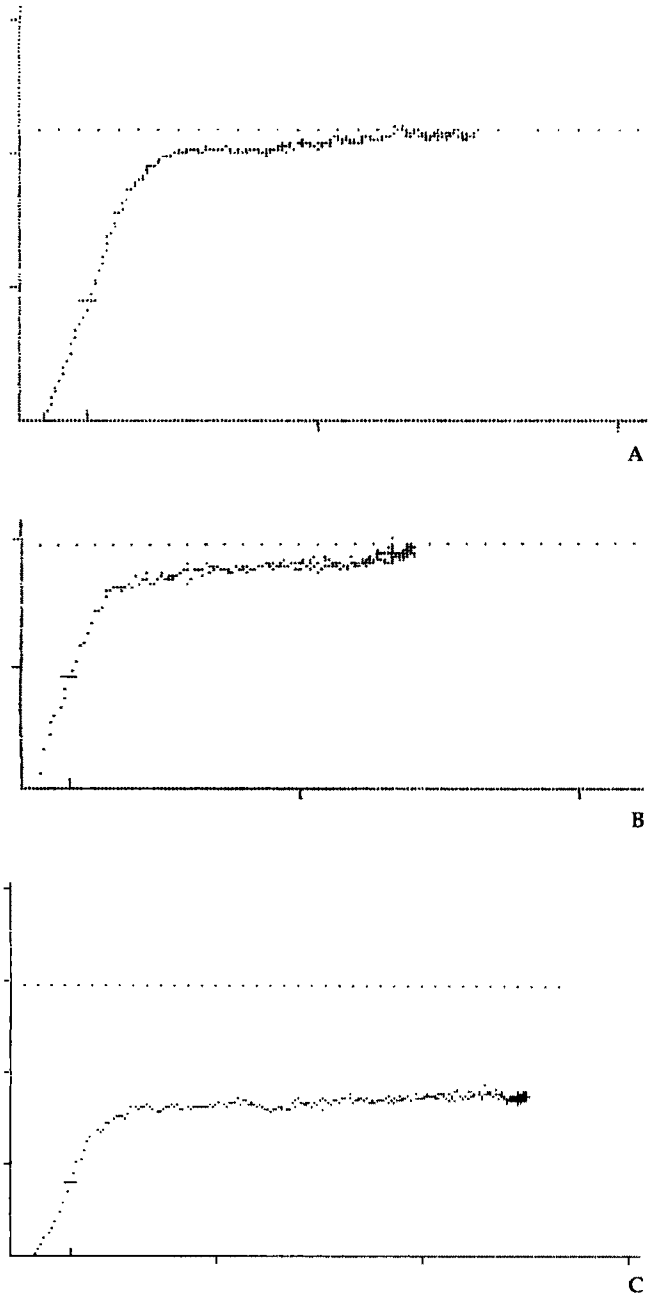

Figure 3. CO_2 single breath tests from (**A**) normal child, (**B**) child with ASD and L–R shunt; (**C**) child with hypoperfusion and R–L shunt. The volume axis is marked 5,10,15% etc. of predicted total lung volume. The markings on the vertical axis are 2, 4, 6, 8% CO_2. The computer has marked in V_Daw with a short horizontal line in phase II, and also on the volume axis.

production, which is a measure of alveolar ventilation, was increased by 1.5% by this maneuver (P = 0.5).

The ten normal children all had small alveolar deadspace fractions, mean plus SD, 0.10 ± 0.03. For the children with hyperperfusion it was 0.13 ± 0.06; the standard deviations but not the means differed significantly (P = 0.05). Four children with PDA or ASD had values more than two standard deviations greater than the mean of the normal children, and the distribution was somewhat skew. Most children with hypoperfusion had greatly increased values for V_Dalv/V_Talv ($P < 0.01$); this group did not overlap with the normal group. The unclassified group also had increased values ($P < 0.004$).

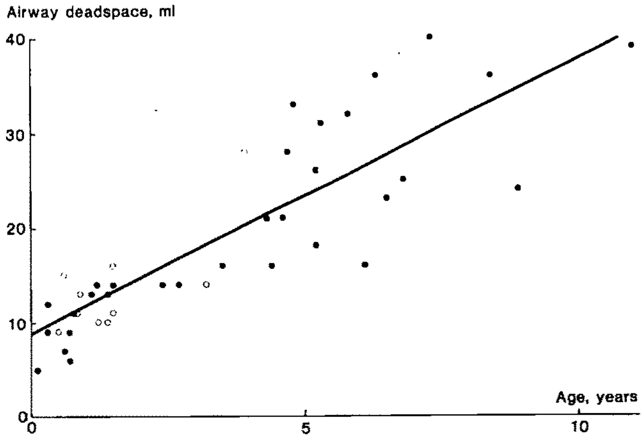

Figure 4. The regression of V_Daw against age for all patients. Those whose height or weight differed from predicted values by more than two SDs are shown with open circles.

The physiologic deadspace fraction, V_Dphys/V_T, was low in both the normal group (0.24 ± 0.05) and in those with hyperperfusion (0.28 ± 0.06, P = 0.1), whereas two of the underperfused children had values larger than 0.5.

The arterial end-tidal P_{CO_2} difference was small among the normal children (mean, 0.35 ± 0.87 torr). In the children with hyperperfusion, it was 0.40 ± 1.40 torr (not significant). The two greatest values were seen in two children with ASD, both of whom had widened pulmonary vasculature on the chest x-ray. Among the hypoperfused children, $Pa_{CO_2}–PET_{CO_2}$ was much increased (range, 2.3–12.8 torr), and there was no overlapping with the control group. Increased values were also seen in the fourth group ($P < 0.08$). Figure 5 shows the relationship between V_Dalv/V_Talv and $(Pa_{CO_2}–PET_{CO_2})/Pa_{CO_2}$. All the values lie below the line of identity, i.e., the alveolar deadspace fraction is always greater than the arterial end-tidal difference suggests.

The phase III slope index was calculated from 100 × increase in F_{CO_2} during phase III divided by mean phase III F_{CO_2}, and is thus corrected for the degree of hyperventilation. Phase III slope index showed very little spread of values in the controls (mean and median, 2.3). The median for the children with hyperperfusion was 3.1 (P = 0.04) with a skew distribution of the greater values, similar to that for V_Dalv/V_Talv. The children with underperfusion showed a very large variation in phase III slope; the steepest

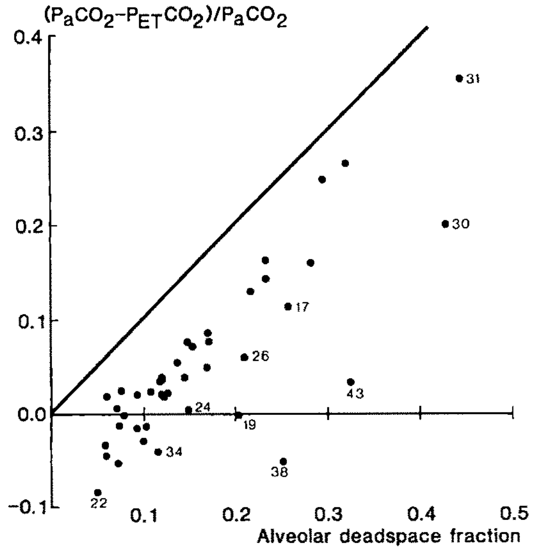

Figure 5. The relationship between alveolar deadspace fraction and (PaCO$_2$–PET$_{CO_2}$/PaCO$_2$. All the points lie below the line of identity. This is because phase III has a positive slope. With the exception of patient 30, all the marked patients, who lie furthest from the line of identity, had pulmonary hyperperfusion.

one was observed in a small infant with PS and TGA who was being given prostaglandins. Four of the children with underperfusion had normal slopes. Among the normal and hyperperfused children, phase III slope index was correlated to V$_D$alv/V$_T$alv (r = 0.74, $P <$ 0.0001). With the remaining children included, r was 0.65 ($P <$ 0.0001).

Arterial oxygenation was excellent in the controls (median PaO$_2$ = 260 mm Hg). In the children with hyperperfusion the median was 203 mm Hg (P = 0.005). Very low values were recorded in the underperfused group.

Rectal temperatures at the time of measurement were 36.2 ± 0.7 °C in the normal and hypoperfused children, 36.0 ± 0.8 °C in the hyperperfused, and 35.3 ± 1.2 °C in the unclassifiable children.

Discussion

The single breath test for CO$_2$ has previously been used to assess lung function in anesthetized infants and children (12). However, we are not aware that on-line corrections have previously been applied. The only error not corrected on-line (it was corrected during the statistical analysis) is the tidal volume dependent underestimate of FE$_{CO_2}$ (Fig. 2). This error is due to inadequate removal of CO$_2$ from the cuvette during inspiration when the analyzer makes a new zero calibration. It is reasonable to assume that other aspects of the system, such as the rebreathing and compressed volume corrections, perform correctly. These errors and their corrections have recently been reviewed (11).

Measurement of gas exchange using the single breath test for CO$_2$ has considerable advantages compared with merely analyzing mixed expired FCO$_2$ collected in a Douglas bag. The latter gives only V$_D$phys/V$_T$ and CO$_2$ production, whereas SBT-CO$_2$ gives in addition V$_D$aw, V$_D$alv/V$_T$alv, phase III slope, and end-tidal CO$_2$— all of which allow better understanding of the nature of gas exchange derangements in heart and lung disease (2,3). SBT-CO$_2$ is especially valuable for observing gas exchange in situations in which the alveolar and airway deadspaces may change independently of one another, e.g., during thoracic surgery (9,10). In addition, monitoring CO$_2$ production provides an index of both metabolism and circulatory function. The breath-to-breath variation in CO$_2$ elimination should not be regarded as a drawback of the system for it reflects genuine variation in lung filling and emptying, presumably due in part to cardiac activity. However, in children V$_D$alv/V$_T$alv can be very small, and its measurement demands a greater degree of accuracy than has previously been needed when only V$_D$phys/V$_T$ was measured. For instance, in a normal child, V$_D$alv/V$_T$alv is 0.10, but a 2% overestimate of PaCO$_2$ will give a value of 0.12. This error combined with a 2% underestimate of PE$_{CO_2}$ will give a value of 0.14. The same errors have proportionately less effect in adults, in whom the alveolar deadspace fraction is larger (5).

In this analysis we have chosen to ignore the apparatus deadspace (usually 9 ml). Thus the values given for V$_D$phys/V$_T$ refer to the intubated child's gas exchange rather than that of child plus apparatus.

The classification into groups was based on preoperative findings, and it is reasonable to expect that the L–R shunts in the children with over circulation will not change direction with the application of intermittent positive pressure ventilation (IPPV). In some children in the unclassified group this assumption is unrealistic: we have seen on several occasions how a pulmonary outflow tract stenosis (in the presence of a VSD) can change in severity during operation, and thus change the shunt from L–R to R–L, with consequent hypoxia and an increase in V$_D$alv.

The Airway Deadspace

The airway deadspace is traditionally difficult to measure. Leakage from the ventilator tubings will reduce V$_D$aw especially if, as here, an end-inspiratory pause is applied. Air tightness was always tested before measurements were taken. Another potential problem is that of delay in analysis of the CO_2 signal. However, compared with that of the flow signal, this delay is of the order of only a few milliseconds (2) if the CO_2 analyzer is equipped with sufficiently powerful components, as it was in this study.

For a given alveolar ventilation, increasing V_T and decreasing frequency or vice versa does not affect V_Daw in adults (5) or children. The probable reason for this is that at the lower frequency, diffusion during the longer EIP causes proximal movement of the alveolar/fresh gas interface before expiration starts (3). This counteracts the increase in airway caliber that the greater tidal volume and end-inspiratory pressure imply. Slightly greater values for V_Daw might therefore have been obtained if a ventilator pattern without an EIP had been used.

Although V_Daw can be made to vary greatly in a given individual (e.g., by holding of the breath) it is relatively constant during IPPV, varying by only about 2–6% from breath to breath during undisturbed anesthesia. (However, turning to the lateral position and maneuvers such as as sternotomy and thoracotomy have important effects on V_Daw (9,10).) Thus, at least in children, if only V_Dphys is known, it is possible to estimate the alveolar deadspace during undisturbed anesthesia by first making an estimate of V_Daw from height or age and subtracting this from V_Dphys. Estimation of V_Dalv is of particular interest in the presence of gross hypo- or hyperperfusion, two causes of increased alveolar deadspace in children. It is interesting to observe that deviations from predicted height and weight appear to have little effect on the relationship between V_Daw and age (Fig. 4).

Alveolar Gas Exchange

The children in the control group demonstrated excellent alveolar gas exchange. According to the isoshunt diagram of Benatar et al. (13) the children had an intrapulmonary shunt of 2–9%. Their alveolar deadspace fractions were low, less than half the value found in middle-aged adults (5), and less than the values for young adults in the study cited above. This efficient alveolar gas exchange, which occurs in spite of inflation pressures greater than those necessary in adults, must reflect the lack of acquired airway disease in children, and perhaps also the smaller vertical height of the lung.

Because V_Dalv/V_Talv is so small, V_Dphys/V_T is also relatively small: mean value 0.26. The adult mean is 0.31–0.44, depending on tidal volume (5). Mean Pa_{CO_2}–PET_{CO_2} was 0.4 torr, also less than in adults. The finding of a small negative arterial end-tidal P_{CO_2} gradient has previously been demonstrated in young adults (5). It can be explained by the fact that Pa_{CO_2} is the temporal and spatial mean Pa_{CO_2}, whereas PET_{CO_2} represents the P_{CO_2} of the last specimen of gas to leave the lung.

Children with pulmonary hyperperfusion did not differ significantly in age, tidal volume, or temperature from the normal children. Mean Pa_{O_2} was, however, significantly lower, corresponding to shunts of about 5–18%, which agrees with findings in the awake state (14). The alveolar deadspace fraction showed a greater spread of values than in the normal children. V_Dphys/V_T was insignificantly increased, and so a "normal" ventilator setting would be expected to give adequate alveolar ventilation. The slope of phase III of SBT-CO_2 was significantly increased. It should be noted that phase III slope is a dimensionless measure and is not dependent on calibration; it may thus be more sensitive to subtle changes in $\dot{V}/\dot{Q}$ relationships than V_Dalv/V_Talv and Pa_{CO_2}–PET_{CO_2}, both of which, as argued above, require extremely accurate measurement of gas and blood P_{CO_2}. Because phase III slope can be increased, it is possible for a child with a clearly increased alveolar deadspace fraction to have a normal arterial end-tidal CO_2 difference (Fig. 5). (Another contributing factor here is the effect of rebreathing, which can be seen to be most marked in the smallest children. Rebreathing affects calculated V_Dalv but not expired P_{CO_2}.) In the pooled hyperperfused and normal children there was a very strong relationship between phase III slope and the alveolar deadspace fraction, just as there is in adults (5). $\dot{V}/\dot{Q}$ mismatching in pulmonary hyperperfusion may be explained by loss of homeostasis at the alveolar/capillary level, which may arise because all available vessels must be kept open in order to accommodate the increased pulmonary flow. Closure of an ASD causes an abrupt, transient increase in $\dot{V}/\dot{Q}$ mismatching (10); this would agree with the loss of homeostasis hypothesis. Among children with overcirculation, there was a negative relationship between Pa_{O_2} and alveolar deadspace fraction ($r = -0.57$, $P = 0.02$). The increased $\dot{V}/\dot{Q}$ spread agrees with the findings by others of increased airway resistance (15,16). However the degree of $\dot{V}/\dot{Q}$ mismatch compared to normal controls is not great: Lees et al. (14) were unable to detect it by studying the urine–alveolar N_2 difference. Increased phase III slope, the increased spread of values for the alveolar deadspace fraction, and the reduced Pa_{O_2} are the most important evidence of $\dot{V}/\dot{Q}$ mismatching in these children.

In children with VSDs and increased pulmonary pressure, the effect on the pulmonary vasculature may be different from that of an ASD, where pulmonary artery pressure may remain low for many years (17).

However, the four children with VSD did not differ from the six children with ASD in alveolar deadspace fraction, phase III slope, or Pa_{O_2} (but they were younger, reflecting the necessity for early VSD repair). There was no correlation between age and any of these variables within the group. In six adults with ASD, ages 37–66 yr, values for these variables were comparable with those of normal adults of the same age (9). Thus the pulmonary vasculature appears to tolerate increased flow, as opposed to pressure, relatively well.

Children with hypoperfusion and R–L shunting presented a single breath test resembling that seen in pulmonary embolism (2,4). That is, phase III had a normal slope but V_Dalv/V_Talv and $Pa_{CO_2}–PET_{CO_2}$ were greatly increased—a parallel deadspace. To what extent this appearance is due on the one hand to true hypoperfusion of lung parenchyma, i.e., high $\dot{V}/\dot{Q}$, or on the other hand to R–L shunting, which raises Pa_{CO_2} above pulmonary end-capillary P_{CO_2}, cannot be determined without sampling left atrial P_{CO_2}. However, it is likely that the shunt plays an important role. A practical consequence is that an increased minute ventilation must be given in order to maintain CO_2 homeostasis. As others (18) have found, these children were hypoxic in spite of normal or reduced Pa_{CO_2} values. End-tidal CO_2 is not a reliable indicator of Pa_{CO_2}: the $Pa_{CO_2}–PET_{CO_2}$ difference can be greater than in most adults.

One child in this group who had a much increased phase III slope (patient 43) was receiving prostaglandins to prevent closure of a PDA. This may have interfered with homeostatic mechanisms, further increasing $\dot{V}/\dot{Q}$ spread. Five hypoperfused children had Pa_{O_2} values below 70 mm Hg in spite of an FI_{O_2} of 0.5. Gas exchange during IPPV in these children does not seem to have been much different from that observed in the awake state by Lees et al. (18).

In the unclassified group, values were often midway between those of the over- and underperfused children: this is not unreasonable when the nature of the lesions is taken into account. The greatest alveolar deadspace fraction and phase III slope in this group were seen in a small child with cardiac failure due to VSD and PDA (patient 43). This child was not included in the hyperperfusion group because of a low Pa_{O_2}. An SF_6 washout curve showed reduced alveolar mixing efficiency, presumably due to fluid retention secondary to the cardiac failure. Cardiac failure in children is associated with increased deadspace (19). Otherwise, increased alveolar deadspace in the unclassified children always occurred in association with a normally sloping phase III, as would be expected with hypoperfusion and an R–L shunt.

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Behavioral Effects of Chronic Exposure to Low Concentrations of Halothane during Development in Rats

Edward D. Levin, PhD, and Robert E. Bowman, PhD

LEVIN ED, BOWMAN RE. Behavioral effects of chronic exposure to low concentrations of halothane during development in rats. Anesth Analg 1986;65:653–9.

Long-term behavioral effects of chronic exposure to low concentrations of halothane were evaluated in rats exposed to low (12.5 ppm) concentrations from day 2 of conception until either 30 (halothane-30) or 60 (halothane-60) days after birth. Rats similarly treated but not exposed to halothane served as controls. When these rats were tested for radial arm maze exploration as adults (1 yr old) both exposure groups showed significant deficits compared with controls. The halothane-treated rats entered significantly fewer arms before reentering an arm (entries-to-repeat). At 55 days of age, in the spontaneous alternation test, response speed was significantly slower than controls in both halothane-30 and halothane-60 rats. This effect was not seen in rats more than 55 days old. Replicating previous results, the halothane-60 rats showed deficits in learning a light–dark discrimination. This deficit was not seen with halothane-30 rats, indicating that continued halothane exposure during the 30- through 60-day period was necessary for inducing a noticeable long-term learning deficit. The results show that chronic exposure of rats to low concentrations of halothane during development results in subsequent behavioral alteration, and that termination of halothane exposure at 30 days of age rather than at 60 days of age avoids some of the signs of behavioral impairment.

Key Words: PSYCHOLOGIC RESPONSES—chronic halothane exposure. ANESTHETICS, VOLATILE—halothane. TOXICITY—halothane.

Since its introduction 30 years ago, halothane has become one of the most widely used general anesthetics. It has been considered relatively safe when patients are acutely exposed to anesthetic concentrations (1), but there is evidence that it may present hazards when operating room personnel are chronically exposed to low concentrations (2). Halothane concentrations in the operating room have been found to range up to 32 parts per million (ppm) in the ambient air (3) and as high as 140 ppm in the anesthetist's work area (4). Being lipophilic, halothane is relatively slowly excreted from the body (5). It crosses the placenta (6) and appears in mother's milk (7), exposing the offspring of pregnant or nursing operating room workers. Some studies have found adverse effects in operating room personnel including reproductive impairments (8,9) and deficits in memory performance (10). However, it is not certain whether these effects were due to halothane exposure or other aspects of the working conditions in the operating room. Animal studies provide an opportunity to study the specific effects of halothane without the confounding factors often present in studies of operating room workers.

Studies using rodent models have found that halothane exposure during development may have particularly severe consequences on the brain and behavior. Chalon et al. (11) found that mice whose mothers had been exposed to 1 or 2% halothane during days 6 and 10 or days 14 and 17 of gestation show long-lasting deficits in spatial maze learning. Quimby et al. (12,13) found a long-lasting learning deficit in rats after developmental exposure starting in utero and lasting until 60 days after birth. They chronically exposed rats to 10 ppm of halothane given on a "working week" schedule of 8 hr/day for 5 days/week. The learning deficit, which was seen when the rats were adults, consisted of retarded acquisition of a light–dark discrimination to escape foot shock in a Y-maze. Their rats also showed a lowered threshold for motor responses to foot shock. However, the learning deficit did not seem to depend on altered foot shock

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Address correspondence to Dr. Levin, Department of Psychology, 405 Hilgard Avenue, University of California at Los Angeles, Los Angeles, CA 90024.

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sensitivity, because there was also a halothane-related deficit in a spatial discrimination task for food reinforcement. Rats exposed to halothane only after reaching adulthood (day 60 through 150) did not differ from controls in either the shock–escape or food-motivated learning tests or foot-shock sensitivity. In another study, Uemura et al. (14) found that exposure to 100 ppm of halothane on the working week schedule from day 2 of gestation until day 60 after birth retarded the development of spontaneous alternation, which is a measure of the rat's natural tendency to explore new places rather than return to old ones. Exposure to 25 ppm continuously did not affect development of spontaneous alternation.

These behavioral alterations have been found to be accompanied by morphologic changes in the brain. Chang et al. (15–17) found that the offspring of pregnant rats exposed to 10 ppm halothane on the "working week" schedule showed ultrastructural damage in cortical pyramidal cells as adults. Quimby et al. (12,13) exposed rats on the same schedule from conception until day 60 postpartum and found impaired development of the synaptic web and postynaptic apparatus in 30% of the cortical synapses of the offspring. Low-level chronic halothane exposure has also been found to cause retarded synaptogenesis (14,18) and impaired dendritic growth (19). These neuronal changes may have resulted from interference with the polymerization of neurofilaments produced by halothane (20) and may underly the observed behavioral effects.

The present study was conducted to determine whether exposure to low concentrations of halothane for a more restricted period during development would also cause behavioral effects. Exposure on the working week schedule from day 2 of conception until 60 days after birth (halothane-60) was compared with exposure from day 2 of conception until 30 days after birth (halothane-30). Although neural development is essentially complete in the rat by 30 days after birth, late developing structures such as the hippocampus still show considerable plasticity during the juvenile period from day 30 to 60 (21). Terminating halothane exposure at day 30 might be early enough to permit completion of neural development that had been inhibited by halothane exposure up to that time. Several behavioral tests were used to examine the effects of these two exposure regimens, including the shock–escape learning test to compare with earlier studies and the 8-arm maze exploration test to evaluate the hypothesis that exposure continuing through the latter part of development might particularly affect the hippocampus.

Methods

Experiments

This study consisted of three experiments. In experiment 1, the halothane exposure (12.5 ppm) lasted from day 2 of gestation until 30 days after birth (halothane-30). In experiment 2, the exposure continued until 60 days after birth (halothane-60). Experiment 3 included both the halothane-30 and halothane-60 exposure groups.

Subjects

Albino rats (Sprague–Dawley; Madison, WI), about 130 days old, were purchased when 2-days pregnant. They were randomly sorted into treatment groups on the day of arrival and housed in litter cages with pine wood shavings. Rat chow (Wayne Lab Blox) and tap water were available ad libitum. A 12-hr/12-hr light–dark schedule was maintained throughout the study, with behavioral testing during the light period. The rats in the halothane groups were housed in exposure chambers. The rats in the chamber control group were also housed in exposure chambers, but no halothane was given. The rats in the room control group were placed in similar-sized cages in the same room as the exposure chambers. When the rat pups were born, litters were pared to eight as nearly sex-balanced as possible. The mothers were removed 25 days after birth. After day 30 the offspring were housed in same-sexed pairs.

Halothane Exposure

Halothane was added to the airstream by a Drager halothane vaporizer. The flow of air and halothane passed through flowmeters to regulate exposure levels. The system was calibrated by gas chromatography. The rats in the halothane groups were exposed to 12.5 ppm of halothane in the air on a working week schedule of 8 hr/day (approximately 9:00 AM to 5:00 PM) for 5 days/week (Monday–Friday). The pregnant rats were exposed from day 2 of conception through parturition. Mothers and pups were exposed from parturition until separation on day 25, and the offspring alone were exposed until either 30 (halothane-30) or 60 days (halothane-60) after birth.

Light–Dark Discrimination

In all three experiments, male rats (150 days of age) were tested in a symmetrical Y-maze on a light–dark discrimination, shock–escape task. In experiment 2, females also were tested. This paradigm was previously found to be sensitive in detecting the effects of chronic exposure of developing rats to low concentrations of halothane (12, 13). The mazes had aluminum walls, stainless steel bar floors, and Plexiglas tops. Each alley was 12 cm high, 12 cm wide, and 45 cm long. The mazes were enclosed in wooden chambers. The cue stimulus at the end of each alley was a 2.5-watt, white light bulb. A pulsed (60 Hz) constant current shock of 1.25 mA was delivered through the floor and walls of the maze as negative reinforcement. Guillotine doors at the threshold of each alley blocked access from the rest of the maze between trials. Photobeams across the alleys 12 cm from the end detected the alley choices. The operation of the mazes during a session and data collection were performed by an Automated Data Systems 1800E computer.

At the beginning of each session, the rat was trapped in one arm of the maze. After 30 sec, the door was raised and the light came on at the end of one of the other two arms. The rat could avert a shock (an avoidance response) by entering the lit arm first within 10 sec. If the rat chose the lit arm first after the onset of the shock, a correct escape response was scored and the shock was turned off. If the rat made an incorrect response, the shock remained on and the door to the start arm was closed, leaving the correct arm as the only remaining choice (correction procedure). After a 30-sec interval with the rat trapped in the correct arm, the next trial was started. The location of correct arms was varied in a counterbalanced pattern. Starting at 150 days of age, sessions of 30 trials were run 5 days/week until the rat reached a criterion of nine avoidance or correct escape responses in ten trials.

Shock Sensitivity

In experiment 2, after the male and female rats completed the shock–escape maze test, their reaction to a range of electric shocks was measured. For a single session, each rat was placed in a Plexiglas chamber (8 × 10 × 31 cm) located in a sound and light attenuated box. The floor of the chamber was made of brass bars through which electric shock was delivered. The force of the rat's muscular reaction was transduced into an analog electrical signal through a diaphragm attached to the chamber floor. This signal was transformed to a digital signal by an Automated Data Systems 1800E computer. During the test session, the rat was given ten different shock levels: 0.025, 0.05, 0.10, 0.15, 0.20, 0.30, 0.40, 0.50, 0.60, and 0.70 mA. These were given 0.2-sec pulses of scrambled shock (60 Hz) at 10-sec intervals in ascending and descending order four times with 2-min intervals between each sequence. The median reaction to each shock level was used for analysis.

Acoustic Startle

In experiment 3, the acoustic startle response was measured in 1-yr-old female controls, halothane-30 rats, and halothane-60 rats. This test used the same apparatus as the shock sensitivity test in Experiment 2. Instead of shock, 0.2-sec pulses of sound (100 dB, 1000 Hz) were presented. Each session included 16 pulses, one every 10 sec. The dependent measure was the force exerted on the floor in response to the acoustic stimulus. Blocks of four responses were averaged for analysis. The rats were tested on three consecutive days.

Spontaneous Alternation

In experiment 2, 120-day-old males and 1-yr-old females in both the control and halothane-60 groups were tested for Spontaneous Alternation (SA). In experiment 3, 55-day-old males and 1-yr-old females in all three groups were tested for SA. In experiment 3, a group of breeders that did not give birth was also tested. Spontaneous alternation was run in a black, wooden T-maze. The maze had a clear Plexiglas top and a concrete floor. The alleys were 9 cm high and 10 cm wide. The stem of the maze and the two choice alleys were each 37 cm long. The stem included a 23-cm long start box separated from the rest of the maze by a guillotine door. The choice alleys also had doors at the choice point. Before each session, the maze was wiped out with a 1% acetic acid solution to help mask odor cues left by previous rats. At the start of each trial, the rat was placed in the start box for 20 sec. The latency for the rat to enter one of the choice arms (four paws beyond the threshold) and the choice were measured. The maximum latency allowed was 300 sec. After making a choice, the rat was trapped in the arm for 30 sec and then was carried to the start box for the next trial. Six trials were run. The dependent measures were percent of choice alternation and response latency. Before analysis, to compensate for a skewed distribution, the latency scores were converted to speed scores of (1/latency).

8-Arm Maze Exploration

In experiment 3, 1-yr-old females from the control, halothane-30, and halothane-60 groups that had not been previously tested were tested for exploration of

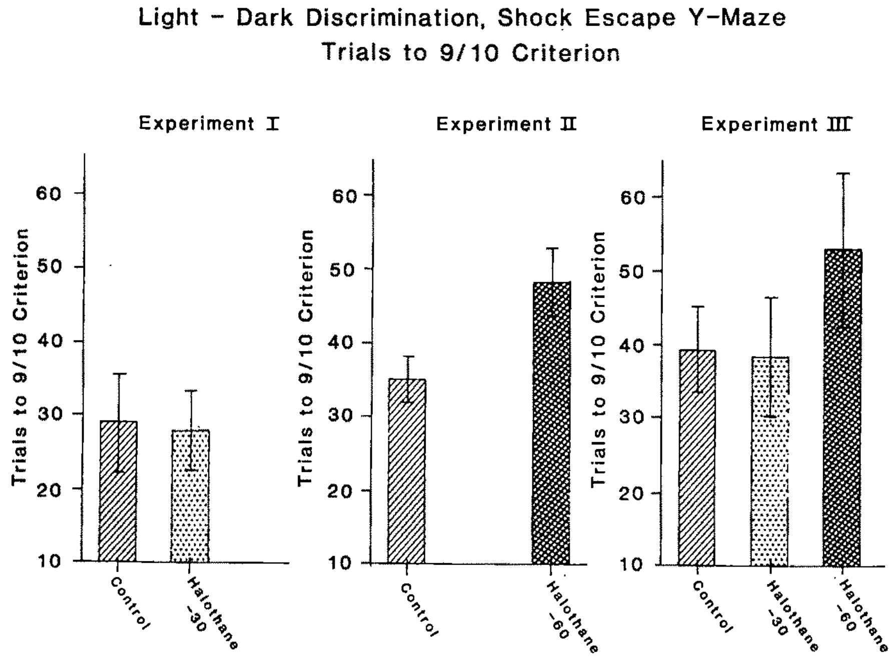

Figure 1. Light–dark discrimination in the shock–escape Y-maze: trials to 9/10 criterion (mean ± SEM), experiments 1, 2, and 3.

an 8-arm maze. The walls of the alleys and the floor of the center platform were made of black painted wood. The floors of the alleys were made of wire mesh. The top of the entire maze was clear Plexiglas. The center platform was 34 cm in diameter, and each of the radial alleys was 10.5 cm wide, 10 cm high, and 42 cm long. To begin each session, the rat was placed on the center platform. The rat's pattern of alley entries (all four feet beyond the threshold) was recorded. The rat was allowed to explore the maze freely until eight entries had been made or 5 min had elapsed. The number of alleys entered before a reentry (entries to repeat) was used as the measure of choice performance. The latency taken to make eight alley entries was also analyzed.

Statistics

In all of the behavioral tests, the control rats were tested at the same time and under the same conditions as the halothane-exposed rats. Order of testing was randomized among the groups. All of the data of the offspring rats were analyzed in terms of litter means to avoid the problem of confounding possible litter effects with experimental effects. Analysis of variance was used to assess the significance of the data. Good's statistic (22) for detecting the effects of low-level toxic effects was used when there was evidence that only some of the rats responded to the treatment.

Results

Body Weight

Halothane exposure did not have a significant effect on adult body weight of the offspring in any of the three experiments. In experiment 3, transient deficits in weight gain were observed during exposure. The halothane-exposed pregnant rats gained 3.4% less weight during gestation, which was reflected in a significant halothane × days interaction [$F(1,45) = 5.94$, $P < 0.05$]. The halothane-exposed offspring weighed 5.6% less than controls 23 days postpartum ($P < 0.10$) and 6.5% less 32 days postpartum ($P < 0.01$). By 65 days of age they were not different from controls in weight.

Light–Dark Discrimination

Trials to 9/10 correct criterion from all three experiments are shown in Figure 1. In experiment 1, there was no significant effect of halothane. Both groups took about 29 trials to reach criterion. In experiment 2, there was a significant deficit [$F(1,7) = 6.25$, $P < 0.05$) in the halothane-60 group, which took 45.9 ± 3.8 trials, whereas the control rats took 34.3 ± 3.4 trials. Both male and female rats showed the effect. Experiment 3 was consistent with experiments 1 and 2. The control and halothane-30 groups did not differ from each other, whereas the halothane-60 group took longer to reach criterion. This difference was not significant by analysis of variance, but examination of the individual data of the halothane-60 group indicated that some rats were impaired, whereas others showed control-level performance. The difference between the control group and the halothane-60 group was significant ($P < 0.05$, one-tailed) when Good's statistic (22) for responders and nonresponders was used. The one-tailed test was considered appropriate because of the previous deficit seen in experiment 2 and by Quimby et al. (12,13).

Shock Sensitivity

There were no significant halothane-related differences in the force of reaction to foot shock in experiment 2. There was a significant main effect of sex, with the females showing greater responsiveness to foot shock [$F(1,7) = 14.61$, $P < 0.01$]. This difference was exacerbated by higher shock levels as was reflected by the significant sex × shock level reaction [$F(9,63) = 7.53$, $P < 0.001$]. At the lowest shock level (0.025 mA), the males showed a greater response than the females, whereas at the highest shock level the females showed about a 20% greater response.

Acoustic Startle

There were no significant halothane-related differences on the acoustic startle test with the halothane-30 and halothane-60 groups in experiment 3. There was a significant habituation effect seen over the daily sessions [$F(2,32) = 16.95$, $P < 0.001$], in which the average response changed from 13,361 ± 290 on the first day to 11,233 ± 290 on the second day to 10,603 ± 258 on the third day. There were no significant within-session habituation effects detected.

Spontaneous Alternation

There were no significant halothane-related effects on the percent alternation. Response speed showed significant halothane-related effects in one cohort but not the other cohorts. There were no significant halothane-related effects on speed in either the 120-day-old or 1-yr-old females of experiment 2 and the adult breeders of experiment 3, but the 55-day-old males of experiment 3 did show a reduction in speed in the halothane-exposed groups [$F(2,37) = 3.37$, $P < 0.05$]. The controls, halothane-30 and halothane-60 groups had means of 65.0 ± 8.6, 32.5 ± 7.2, and 48.6 ± 9.9, respectively.

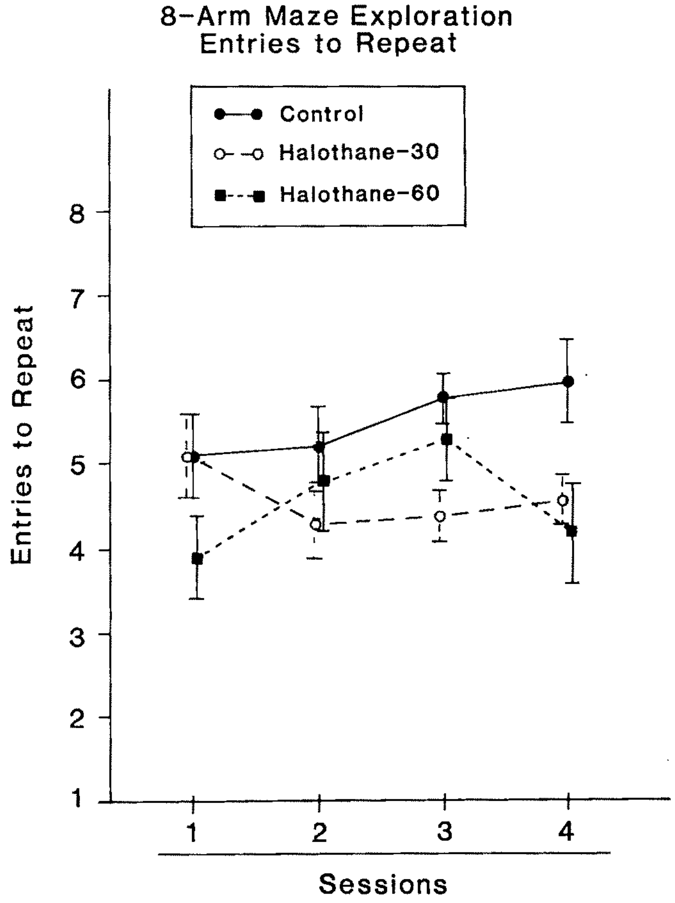

Figure 2. 8-Arm maze exploration: entries to repeat (mean ± SEM), experiment 3.

8-Arm Maze Exploration

In experiment 3, both the halothane-30 and halothane-60 groups had significantly lower entries-to-repeat scores than did control rats [$F(2,20) = 3.80$, $P < 0.05$]. Control rats took 5.56 ± 0.28 entries to repeat, whereas the halothane-30 group took 4.56 ± 0.15, and the halothane-60 group took 4.57 ± 0.36 entries (Fig. 2). There were no significant effects of session or halothane × session. There were no significant halothane-related effects on response latency.

Discussion

As seen in earlier studies (12–14), chronic exposure to low levels of halothane during development in these experiments resulted in selective, long-lasting behavioral alterations. Both the halothane-30 and halothane-60 exposure paradigms had behavioral consequences, but the exposure lasting until 60 days after birth had effects in more tests. The 8-arm maze entries-to-repeat measure and the spontaneous alternation speed measure detected significant effects with both exposure conditions. The halothane-induced effect on 8-arm maze performance was detected at 1 yr of age, whereas the decrease in SA speed was seen at 55 days but not beyond that age. The shock–escape, light–dark discrimination test at 150 days of age detected effects in the halothane-60 groups but not in the halothane-30 groups. Stopping exposure at 30 days may have allowed sufficient time for enough developmental recovery to occur in the halothane-30 group so that they were able to perform this task.

The effect on entries-to-repeat in the 8-arm maze at more than 10 months after the end of exposure was quite long-lasting and may have represented a permanent result of exposure to halothane during development of the central nervous system. This measure of exploratory behavior may have wider utility in behavioral toxicology. It has also been found to be sensitive in detecting the effects of chronic exposure to low concentrations of lead (10 or 100 ppm) in weanling rats (23). Exploration in the 8-arm maze was more sensitive to halothane than spontaneous alternation in the T-maze. The latter did not detect a significant effect of either halothane exposure regimen, even though it did detect effects of higher exposure levels in another experiment from our laboratory (14). The greater sensitivity of the 8-arm maze test may have resulted from the greater number of alternatives for exploration than the two choice T-maze.

The multiple response locations in the 8-arm maze test makes entries-to-repeat a useful measure for differentiating perseveration and distribution of responses from random responding. Early in the session, random selection of previously visited arms is unlikely. Repetition at this point indicates perseverative tendencies. As more alleys are visited, the chance of randomly choosing a novel alley decreases. High scores indicate distributive tendencies. The random change probability occurrence of entries to repeat scores of 1–8 is: 0.125, 0.219, 0.246, 0.205, 0.128, 0.058, 0.017, and 0.002. The mean entries-to-repeat score expected by chance is 3.24. In this study, all groups performed well above chance. The halothane-exposed groups performed closer to chance than controls. The halothane-exposed groups showed no indication of perseverative choices but did show lessened distribution of responses. This did not appear to be due to decreased use of perseverative turning strategies by the exposed groups. None of the groups significantly differed from each other or exceeded the random chance probability of 25% of choosing adjacent alleys.

The shock–escape maze learning deficit seen in the halothane-60 groups replicated the results of Quimby et al. (12,13). The halothane-30 groups showed similar trials to criterion scores as the controls in both experiments 1 and 3. Continued halothane exposure during the 30–60 day period appeared necessary to produce a deficit on this test. Even though nearly all neural development is concluded in the rat by 30 days after birth, there remains considerable neural plasticity during the juvenile period. McWilliams and Lynch (21) have found that hippocampal reactive synaptogenesis is still quite efficient at replacing lost synapses in the 30–60 day period. Low-level halothane exposure recently has been found to suppress synaptogenesis in both the hippocampus and cortex (19). Ending halothane exposure on day 30 may have allowed sufficient time for recovery from earlier halothane-induced neuronal effects before the developmental window had passed.

The present results provide further indication that chronic, low-level exposure to halothane during development causes long-lasting behavioral alteration. The changes seen at 1 year of age are likely to represent permanent effects. The impaired performance of the halothane-60 groups compared with the halothane-30 groups on light–dark discrimination indicated that continued exposure during the juvenile period was necessary for some aspects of halothane's behavioral effect. Given its properties of inhibiting synaptogenesis and retarding the outgrowth of the dendritic tree (14, 19), halothane may be useful as a tool for examining the developmental windows for many types of behavior. The behavioral effect seen in the halothane-30 group suggests that low-level halothane exposure during development may have adverse behavioral effects, even when the exposure is stopped soon after weaning. The offspring of women operating room workers who are exposed to halothane in utero and through nursing may be at risk for adverse behavioral effects.

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1986;65:660–6

Partial Preservation of Cerebral Vascular Responsiveness to Hypocapnia during Isoflurane-Induced Hypotension in Dogs

Alan A. Artru, MD

ARTRU AA. Partial preservation of cerebral vascular responsiveness to hypocapnia during isoflurane-induced hypotension in dogs. Anesth Analg 1986;65:660–6.

This study was undertaken to determine whether the cerebral vascular response to hypocapnia is preserved during isoflurane-induced hypotension. In six dogs (group 1) cerebral vascular resistance and cerebral blood flow were determined at normocapnia ($Pa\text{CO}_2$ 40 mm Hg) and at hypocapnia ($Pa\text{CO}_2$ 20 mm Hg) while mean arterial pressure was normal, and then again during isoflurane-induced hypotension to a mean arterial pressure of 50 mm Hg. Hypocapnia increased cerebral vascular resistance and decreased cerebral blood flow during both normotension and isoflurane-induced hypotension. However, the magnitude of these responses was greater when mean arterial pressure was normal. In another six dogs (group 2), CO_2 responsiveness was examined during isoflurane-induced hypotension without prior determination of CO_2 responsiveness at normal mean arterial pressure and during sodium nitroprusside-induced hypotension to a mean arterial pressure of 50 mm Hg. As in group 1, partial preservation of CO_2 responsiveness was observed during isoflurane-induced hypotension; the magnitude of the response in group 2 during isoflurane-induced hypotension was similar to that in group 1. In contrast, in group 2 during sodium nitroprusside-induced hypotension, hypocapnia caused no significant change of cerebral vascular resistance or cerebral blood flow. It is concluded that cerebral vessels respond to changes in $Pa\text{CO}_2$ differently during isoflurane-induced hypotension than during hypotension with other commonly used hypotensive treatments. Hypocapnia decreases cerebral blood flow during isoflurane-induced hypotension and, therefore, may also decrease cerebral blood volume, brain bulk, and intracranial pressure.

Key Words: ANESTHETICS, VOLATILE—isoflurane. ANESTHETIC TECHNIQUES—hypotension. BRAIN—blood flow, cerebral vascular resistance. CARBON DIOXIDE—hypocapnia.

Previous studies have reported that cerebral blood flow (CBF) responses to hypocapnia are lost during hypotension induced by drugs and techniques commonly used during anesthesia. In dogs, hypocapnia ($Pa\text{CO}_2$ 20 mm Hg) caused no significant change in CBF or cerebral vascular resistance (CVR) during hypotension (mean arterial pressure 50 mm Hg) induced by sodium nitroprusside (1), trimethaphan (1), or nitroglycerin (2). The absence of cerebral vascular responses to CO_2 was also observed during halothane-induced hypotension to a mean arterial pressure (MAP) of 45 mm Hg in baboons (3), and during hypotension to an MAP of 36 mm Hg induced by combining trimethaphan and halothane in cats (4).

Recently, isoflurane (2–3% inspired concentration) has been proposed as a means for inducing controlled hypotension in patients (5,6). It is not known whether CBF responses to hypocapnia are also lost during isoflurane-induced anesthesia. Currently available data suggest that cerebral vascular responsiveness to CO_2 may be preserved. Drummond and Todd examined CBF responses to CO_2 in normotensive cats (7). They reported a steeper $Pa\text{CO}_2$–CBF regression slope during anesthesia with 1.0 MAC isoflurane than during anesthesia with 1.0 MAC halothane or during sedation with nitrous oxide. Because cerebral vascular responsiveness to CO_2 is enhanced by 1.0 MAC isoflurane at normotension, it is possible that some CO_2 reactivity may persist at higher concentrations of isoflurane used to produce hypotension. If so, isoflurane would be distinguished from such currently used hypotensive agents as sodium nitroprusside, halothane, trimethaphan, and nitroglycerin.

Preservation of CBF responses to hypocapnia during isoflurane-induced hypotension would be important clinically because hypocapnia could be used to decrease CBF and cerebral blood volume (CBV), thereby influencing intracranial pressure when the cranium is closed, brain "bulk" when the cranium is opened, and regional brain tissue perfusion. Hypocapnia rou-

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Address correspondence to Dr. Artru, Department of Anesthesiology, University of Washington School of Medicine, Seattle, WA 98195.

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tinely is used for these purposes during normotension but becomes ineffective when other currently used hypotensive agents are used to lower MAP to ≤50 mm Hg (1–4).

The present study was designed to examine the cerebral vascular response to hypocapnia at normotension and during isoflurane-induced hypotension in dogs. The level of hypotension chosen for study was an MAP of 50 mm Hg. This value is within a range used clinically for elective, controlled hypotension (8). At higher MAP, intact CO_2 responsiveness might be expected with all hypotensive techniques (4,9,10). At lower MAP severe cerebral metabolic disturbances may occur (11).

Methods

Twelve unmedicated mongrel dogs (12.2–20.9 kg) were anesthetized with isoflurane (>1.6%) and N_2O (66%) in oxygen. The trachea was intubated and ventilation was controlled with a Harvard pump. Ventilation was adjusted along with the inspired oxygen concentration to maintain initial blood gas tensions (Radiometer BMS3 MK2 electrodes) at $Pa_{O_2} > 120$ mm Hg and $Pa_{CO_2} = 40 \pm 1$ mm Hg (mean ± SEM). With the animal in the lateral position, a urinary catheter was placed and both femoral veins were cannulated for fluid and drug administration. Intravenous infusion of succinylcholine, 50–120 mg/hr, maintained muscle relaxation. The right femoral artery was cannulated for arterial blood sampling for blood gas analysis and continuous monitoring of systemic arterial pressure and heart rate. Mean arterial pressure was determined by electronic integration. Expired CO_2 was continuously monitored via a Beckman LB-2 medical gas analyzer. Temperature was monitored by a nasopharyngeal thermistor probe and maintained at 37.0 ± 0.5°C by heat lamps. Depletion of vascular volume was minimized by continuous infusion of saline 4–6 $ml{\cdot}kg^{-1}{\cdot}hr^{-1}$.

The animal was then turned to the prone position and the head slightly elevated and fixed in a stereotaxic frame. The zero reference for the strain gauge to measure systemic arterial pressure was set at the level of the top of the dog's head. The method for measurement of CBF was previously described in detail (12) and is summarized here. The sagittal sinus was exposed via craniectomy and, following systemic intravenous infusion of heparin, 8000 units, the posterior sagittal sinus was incised and a snug-fitting, tapered catheter (2 mm internal diameter) was passed anteriorly 2–4 mm. The sinus was packed with strips of Surgicel (absorbable hemostat; Johnson & Johnson, New Brunswick, NJ) through another incision just posterior to the catheter, assuring total diversion of sagittal sinus flow. The tip of the catheter was placed at the level of the base of the skull, and flow from the catheter was collected by gravity in a reservoir and returned by a pump to the femoral vein. At each experimental condition CBF, expressed as ml/min, was determined by three to five timed collections of outflow from the sagittal sinus catheter. Conversion of CBF values from ml/min to $ml{\cdot}min^{-1}{\cdot}100\ g^{-1}$ was based on the portion of the brain that contributed to sagittal sinus flow, namely, 48%. This value was determined as previously described (12) using an additional group of six dogs (1). The accuracy of this method for determining CBF was previously reported for CBF values of 25–98 $ml{\cdot}100\ g^{-1}{\cdot}min^{-1}$ (12) and for CBF values of 30–230 $ml{\cdot}100\ g^{-1}{\cdot}min^{-1}$ produced by altering Pa_{CO_2} (13). CVR was calculated as the ratio of MAP and CBF. At each experimental condition a single sagittal sinus blood sample for measurement of cerebral venous oxygen tension (Pss_{O_2}) was drawn into a syringe through a side-arm at the tip of the sagittal sinus outflow catheter by gentle aspiration.

Table 1. Summary of Experimental Values

Condition	Pa_{CO_2} (mm Hg)	MAP (mm Hg)	Duration (min)
1	40	Normal	30
2	20	Normal	30
3	40	Normal	60
4	40	50	30
5	20	50	30

After completion of the surgical preparation, the expired concentration of isoflurane was decreased to 0.3% (end-tidal concentration determined by gas chromatography) (14). Once stable measurements of cerebral and systemic variables were obtained (at least 25 min later), the 12 animals were divided into two groups of six dogs each. In group 1, CBF was determined during both normocapnia and hypocapnia ($Pa_{CO_2} = 20$ mm Hg) at normotension, and then again at hypotension (see Table 1 for sequence). For each 30-min treatment period, 25 min were allowed for achieving and maintaining the desired condition, and the final 5 min were used to determine cerebral and systemic variables. At condition 3, 55 min were allowed for restoration of normal brain extracellular fluid acid–base balance after the preceding hypocapnia (15). At conditions 4 and 5, hypotension to an MAP of 50 mm Hg was achieved by increasing the inspired concentration of isoflurane to 2.5–4.3%.

In group 2, CBF was determined during both normocapnia or hypocapnia at isoflurane-induced hypotension to an MAP of 50 mm Hg without prior

Table 2. Effect of Hypocapnia on Cerebral and Systemic Variables at Normal MAP in Group 1

Variables	Normocapnia/normotension (condition 1)	Normotension/hypocapnia (condition 2)
Cerebral		
CVR (mm Hg/ml·min^{-1}·100 g^{-1})	1.30 ± 0.34	2.36 ± 0.71^a
CBF (ml·min^{-1}·100 g^{-1})	81.4 ± 21.3	46.2 ± 13.7^a
$PssO_2$ (mm Hg)	58 ± 11	34 ± 7^a
Systemic		
MAP (mm Hg)	106 ± 12	108 ± 13
Heart rate (beats/min)	115 ± 15	132 ± 19
$PaCO_2$ (mm Hg)	41.0 ± 2.7	22.4 ± 1.7^a
PaO_2 (mm Hg)	143 ± 31	150 ± 32
pH	7.34 ± 0.04	7.49 ± 0.04^a
Bicarbonate (mEq/L)	21.7 ± 1.8	17.0 ± 2.1^a
Hemoglobin (g/dl)	13.8 ± 1.5	13.8 ± 1.7
Temperature (nasopharyngeal, °C)	37.3 ± 0.3	37.2 ± 0.3

All values are mean ± SD.
$n = 6$.
Abbreviations: CVR, cerebral vascular resistance; CBF, cerebral blood flow; $PssO_2$, sagittal sinus blood oxygen tension; MAP, mean arterial pressure.
^{a}Significant differences from normocapnia and normotension, $P < 0.05$.

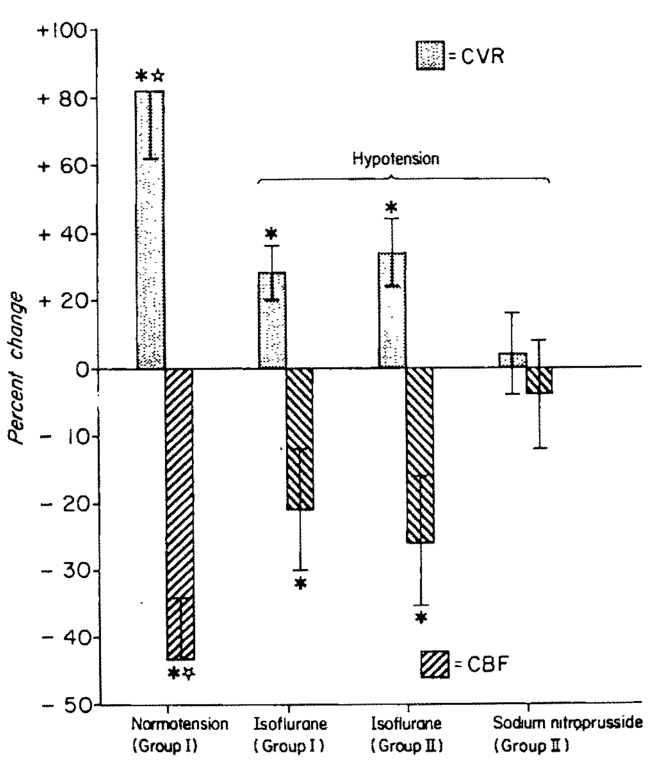

Figure 1. The effect of hypocapnia on cerebral vascular resistance (CVR) and cerebral blood flow (CBF) is shown for each condition of normotension and hypotension. The percent change in CVR and CBF caused by hypocapnia was calculated based on values for CVR and CBF at $PaCO_2$ = 40 mm Hg and either normotension or hypotension. Stippled bars represent CVR, hatched bars represent CBF, and vertical lines denote standard deviation. Hypocapnia caused a significant increase of CVR and decrease of CBF during normotension and during isoflurane-induced hypotension (asterisk, $P < 0.05$), but not during sodium nitroprusside-induced hypotension. The magnitude of changes in CVR and CBF was greater during normotension than during isoflurane-induced hypotension (star, $P < 0.05$).

testing at normotension. These studies were undertaken to rule out the possibility that in group 1 the CBF response to normocapnia and hypocapnia during hypotension was influenced either by time (2 hr elapsed before hypotension was induced) or by the 30-min exposure to hypocapnia at normal MAP. In group 2, three dogs were examined first at normocapnia and then at hypocapnia, whereas the other three dogs were examined first at hypocapnia and then at normocapnia. As in group 1, the duration of each condition was 30 min. The concentration of isoflurane was then decreased to 0.3% and dogs were maintained at normocapnia and normotension for 60 min. After this 60-min period, CBF was again determined during both normocapnia and hypocapnia, this time in conjunction with sodium nitroprusside-induced hypotension to an MAP of 50 mm Hg. These studies were undertaken to determine whether CBF responses to hypocapnia would be absent during hypotension induced solely with sodium nitroprusside as reported in an earlier study in dogs (1). Again three dogs were examined first at normocapnia and then at hypocapnia; another three dogs were examined first at hypocapnia and then at normocapnia. The duration of each condition was 30 min.

Cerebral and systemic variables were compared within groups using repeated-measures two-factors analysis of variance, with $PaCO_2$ and MAP comprising the two treatments (16). Where the calculated F value exceeded the critical value for the 0.05 probability level, a paired t-test with the Bonferroni correction was used to determine which treatment differences were significant. $P < 0.05$ was considered statistically significant.

Table 3. Effect of Hypocapnia on Cerebral and Systemic Variables during Isoflurane-Induced Hypotension in Group 1

Variables	Normotension/normocapnia (condition 3)	Hypotension/normocapnia (condition 4)	Hypotension/hypocapnia (condition 5)
Cerebral			
CVR (mm Hg/ml·min^{-1}·100 g^{-1})	1.57 ± 0.21	0.98 ± 0.13[a]	1.25 ± 0.13[b]
CBF (ml·min^{-1}·100 g^{-1})	72.9 ± 13.1	50.0 ± 6.5[a]	39.4 ± 4.8[b]
Pss_{O_2} (mm Hg)	48 ± 6	50 ± 7	35 ± 5[b]
Systemic			
MAP (mm Hg)	113 ± 17	48 ± 1[a]	49 ± 2
Heart rate (beats/min)	112 ± 23	126 ± 19	126 ± 17
Pa_{CO_2} (mm Hg)	41.9 ± 2.4	41.9 ± 2.6	23.9 ± 1.9[b]
Pa_{O_2} (mm Hg)	145 ± 28	141 ± 26	144 ± 32
pH	7.28 ± 0.03	7.26 ± 0.03	7.43 ± 0.04[b]
Bicarbonate (mEq/L)	19.4 ± 2.1	18.6 ± 1.9	15.8 ± 1.7[b]
Hemoglobin (g/dl)	13.4 ± 1.3	13.5 ± 1.2	13.5 ± 1.2
Temperature (nasopharyngeal, °C)	36.8 ± 0.3	36.9 ± 0.3	36.8 ± 0.3

All values mean ± SD.
$n = 6$.
Abbreviations: CVR, cerebral vascular resistance; CBF, cerebral blood flow; Pss_{O_2}, sagittal sinus blood oxygen tension; MAP, mean arterial pressure.
[a] Significant difference from normotension and normocapnia, $P < 0.05$.
[b] Significant difference from hypotension and normocapnia, $P < 0.05$.

Results

Group 1

At normal MAP cerebral vessels responded vigorously when Pa_{CO_2} was lowered. Hypocapnia increased CVR by 82%, and decreased CBF by 43% and Pss_{O_2} by 41% (Table 2, Figure 1). Cerebral vessels also responded to hypocapnia during isoflurane-induced hypotension, though the magnitude of the response was less than that observed at normal MAP. At MAP of 50 mm Hg hypocapnia increased CVR by 28%, and decreased CBF by 22% and Pss_{O_2} by 30% (Table 3). The end-expired concentration of isoflurane was 2.40 ± 0.31% (mean ± SD) at an MAP of 50 mm Hg.

Group 2

The cerebral vascular response to hypocapnia during isoflurane-induced hypotension was similar in this group (dogs not previously tested for CO_2 responsiveness at normal MAP) to the response in dogs that were first tested for CO_2 responsiveness at normal MAP (group 1). At an MAP of 50 mm Hg, hypocapnia increased CVR by 34%, and decreased CBF by 27% and Pss_{O_2} by 24% (Table 4). In this group isoflurane-induced hypotension to an MAP of 50 mm Hg was achieved with an end-expired isoflurane concentration of 2.28 ± 0.23%. When hypotension to the same level was subsequently produced using sodium nitroprusside, hypocapnia caused no statistically significant change in CVR or CBF (Table 5).

Hypocapnia was associated with increase in blood pH and decrease in serum bicarbonate in all dogs. The magnitude of these changes was similar in dogs at normal MAP to that in dogs during isoflurane- or sodium nitroprusside-induced hypotension. In group 1, hypotension at normocapnia decreased CVR and CBF. Otherwise, neither hypotension alone nor hypocapnia plus hypotension significantly altered other cerebral or systemic variables.

Discussion

Partial preservation of cerebral vascular responsiveness to hypocapnia during isoflurane-induced hypotension sets isoflurane apart from most other hypotensive techniques commonly used in clinical practice. Loss of cerebral vascular responsiveness to hypocapnia has been reported during hypotension to an MAP ≤ 50 mm Hg achieved with sodium nitroprusside (1), trimethaphan (1,4), nitroglycerin (2), and halothane (3). Loss of CO_2 responsiveness has also been reported during hypotension to MAP ≤ 50 mm Hg produced by hemorrhage (17,18) and during hypotension induced with nimodipine (19). In contrast, preservation of CO_2 responsiveness, though again at a lower magnitude than CO_2 responsiveness at normal MAP, has been reported with one hypotensive treatment recently proposed for clinical use (20,21). Boarini et al. reported that in dogs hypocapnia (Pa_{CO_2} of 20 mm Hg) during hypotension (MAP of 50 mm Hg) induced with adenosine resulted in a small but statistically significant reduction in regional CBF, most notably in cerebral cortex (22). However, in no areas was CBF lowered to ischemic levels.

Partial preservation of CO_2 responsiveness suggests that during isoflurane-induced hypotension hypocapnia may be used to alter CBV and CBF. In the

Table 4. Effect of Hypocapnia on Cerebral and Systemic Variables during Isoflurane-Induced Hypotension in Group 2

Variables	Hypotension/normocapnia (condition 1)	Hypotension/hypocapnia (condition 2)
Cerebral		
CVR (mm Hg·ml^{-1}·min^{-1}·100 g^{-1})	0.97 ± 0.22	1.30 ± 0.21^a
CBF (ml·min^{-1}·100 g^{-1})	54.4 ± 13.7	39.7 ± 8.9^a
$Psso_2$ (mm Hg)	49 ± 8	37 ± 5^a
Systemic		
MAP (mm Hg)	50 ± 2	51 ± 1
Heart rate (beats/min)	124 ± 8	125 ± 4
$Paco_2$ (mm Hg)	40.6 ± 1.3	22.3 ± 2.2^a
Pao_2 (mm Hg)	150 ± 9	165 ± 24
pH	7.29 ± 0.06	7.49 ± 0.09^a
Bicarbonate (mEq/L)	19.4 ± 2.4	16.8 ± 1.6^a
Hemoglobin (g/dl)	12.6 ± 0.7	12.6 ± 0.8
Temperature (nasopharyngeal, °C)	36.7 ± 0.2	36.7 ± 0.2

All values are mean ± SD.
$n = 6$.
Abbreviations: CVR, cerebral vascular resistance; CBF, cerebral blood flow; $Psso_2$, sagittal sinus blood oxygen tension; MAP, mean arterial pressure.
[a] Significant differences from hypotension and normocapnia, $P < 0.05$.

Table 5. Effect of Hypocapnia on Variables during Sodium Nitroprusside-Induced Hypotension in Group 2

Variables	Normotension/normocapnia (condition 3)	Hypotension/normocapnia (condition 4)	Hypotension/hypocapnia (condition 5)
Cerebral			
CVR (mm Hg·ml^{-1}·min^{-1}·100 g^{-1})	1.46 ± 0.22	0.95 ± 0.15^a	0.99 ± 0.17
CBF (ml·min^{-1}·100 g^{-1})	75.3 ± 10.5	52.6 ± 8.9^a	50.5 ± 7.3
$Psso_2$ (mm Hg)	44 ± 6	46 ± 6	40 ± 4^b
Systemic			
MAP (mm Hg)	110 ± 15	50 ± 1^a	50 ± 1
Heart rate (beats/min)	112 ± 20	132 ± 14	133 ± 14
$Paco_2$ (mm Hg)	39.6 ± 2.2	39.8 ± 2.2	21.7 ± 1.7^b
Pao_2 (mm Hg)	158 ± 19	149 ± 16	162 ± 16
pH	7.27 ± 0.05	7.27 ± 0.04	7.45 ± 0.05^b
Bicarbonate (mEq/L)	18.3 ± 2.1	18.7 ± 1.9	15.9 ± 2.0^b
Hemoglobin (g/dl)	12.4 ± 0.9	12.3 ± 0.8	12.1 ± 0.7
Temperature (nasopharyngeal, °C)	36.9 ± 0.2	36.8 ± 0.2	36.8 ± 0.2

All values are mean ± SD.
$n = 6$.
Abbreviations: CVR, cerebral vascular resistance; CBF, cerebral blood flow; $Psso_2$, sagittal sinus blood oxygen tension; MAP, mean arterial pressure.
[a] Significant difference from normotension and normocapnia, $P < 0.05$.
[b] Significant difference from hypotension and normocapnia, $P < 0.05$.

case of CBV, hypocapnia should exert a beneficial effect. During isoflurane-induced hypotension, hypocapnia may be used to reduce brain mass, thus decreasing intracranial pressure when the skull is closed, and improving brain compliance and surgical exposure when the skull is opened.

In contrast, the effect of hypocapnia on CBF may be potentially hazardous. Michenfelder and colleagues found that deterioration of cerebral metabolism resulted when animals were hyperventilated during both anemia (23) or focal ischemia (24). It was suggested that hypocapnia-induced decrease of CBF may aggravate already existing reduced oxygen/substrate delivery. Eklöf et al. reported that lowering CBF by carotid artery ligation during hypotension to an MAP of 70 mm Hg caused a deterioration of cerebral metabolism in rats that was not observed with either carotid artery ligation or hypotension alone (25–27). These results raise the concern that hypocapnia-induced decrease of CBF during isoflurane-induced hypotension may similarly disturb cerebral metabolism, indicating that the potential for brain tissue injury exists. However, in no instances in the present study did CBF or $Psso_2$ decrease to values previously reported as "critical," namely, a decrease in CBF to less than 50% of control (25) or to an absolute value of 18–24 ml·100 g^{-1}·min^{-1} (28,29), or a decrease in $Psso_2$ to less than 17–25 mm Hg (23,26). Although it is reassuring that CBF or Pss_{O_2} did not decrease to critical values with hypocapnia during isoflurane-induced hypotension, it should be noted that the present model measures global CBF (primarily cortical) (12,13). Thus the possibility remains that hypocapnia during isoflurane-induced hypotension may result in areas of focal ischemia.

The reason(s) for preservation of CO_2 responsiveness during isoflurane-induced hypotension, but not during hypotension induced by other techniques, is not clear. Isoflurane is reported to be a relatively weak dilator of cerebral vessels (30,31). Assuming that the direct effect of induced hypotension on cerebral vessels is responsible for controlling cerebral vascular tone, isoflurane may cause hypotension without fully dilating cerebral vessels, thereby leaving the cerebral vessels reactive to Pa_{CO_2} change. On the other hand, if reflex cerebral vasodilation secondary to hypotension is the primary factor controlling cerebral vascular tone, isoflurane may oppose that reflex; thereby leaving cerebral vessels incompletely dilated and thus reactive to Pa_{CO_2} change. A third possibility is that isoflurane enhances the mechanism of cerebral reactivity to changes in Pa_{CO_2}, allowing hypocapnia-induced vasoconstriction to override the cerebral vasodilation that occurs with hypotension. Consistent with this mechanism is the report by Drummond and Todd that the responsiveness of cerebral vessels to changes in Pa_{CO_2} was enhanced in cats anesthetized with isoflurane compared with the responsiveness in cats under halothane anesthesia or nitrous oxide sedation (7). Further investigation is needed to determine the means by which isoflurane influences CO_2 responsiveness of cerebral vessels.

The present study was designed to eliminate the possibility that the degree of CO_2 responsiveness in group 1 during isoflurane-induced hypotension was altered because the surgical preparation deteriorated after 2 hr or because 30-min hypocapnia at normal MAP changed subsequent CO_2 responsiveness due to adaptation of brain extracellular fluid pH. Thus in group 2 CO_2 responsiveness during isoflurane-induced hypotension was measured as soon as systemic and cerebral variables stabilized after surgical preparation and without prior testing for CO_2 responsiveness at normal MAP. The observation in group 2 of partial preservation of the cerebral vascular response to hypocapnia during isoflurane-induced hypotension confirms the results in group 1 and suggests that these results were not influenced by the duration of the study or by the earlier exposure to hypocapnia and normotension. The observation in group 2 of absent cerebral vascular response to hypocapnia during sodium nitroprusside-induced hypotension demonstrates that when hypotension is produced and little isoflurane is present, CO_2 responsiveness is abolished. These results are consistent with an earlier report that sodium nitroprusside-induced hypotension to an MAP of 50 mm Hg abolished the cerebral vascular response to hypocapnia in dogs anesthetized with halothane, 0.2% (end-tidal concentration) (1).

The present study was designed so that dogs in group 1 were tested for CO_2 responsiveness at normal MAP before testing for CO_2 responsiveness during hypotension. That hypocapnia increased CVR by 82% and decreased CBF by 43% at normal MAP is consistent with previous studies and suggests both that the cerebral vasculature in these dogs was normally reactive to CO_2 and that the present surgical preparation was suitable to measure those responses (1,2,17). Also observed in the present study was a decrease of CVR in all dogs when MAP was lowered to 50 mm Hg, which suggests that the present experimental preparation preserved normal cerebral vasodilatory responses to hypotension as well as CO_2 responsiveness. Decrease of CBF in the presence of an MAP of 50 mm Hg suggests that this level of MAP was below the lower limit of autoregulation of CBF for dogs. This observation is in agreement with determinations of the lower limit of autoregulation of CBF for dogs during normocapnia (32–34).

In summary, the present results suggest that cerebral vascular responsiveness to hypocapnia is partially preserved during isoflurane-induced hypotension. A beneficial effect on CBV may accrue, so that hypocapnia might be useful for decreasing brain mass during isoflurane-induced hypotension. On the other hand, a deleterious effect may occur if a hypocapnia-induced decrease of CBF causes ischemia. Further studies are needed to examine the mechanism(s) by which isoflurane influences cerebrovascular CO_2 responsiveness to changes in Pa_{CO_2} and to assess the impact on brain integrity of hypocapnia during isoflurane-induced hypotension.

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Endotracheal Tube Leak Pressure and Tracheal Lumen Size in Swine

David A. Finholt, MD, Steven M. Audenaert, MD, Joseph A. Stirt, MD, Kenneth L. Marcella, DVM, Henry F. Frierson Jr, MD, Larry T. Suddarth, and Russell C. Raphaely, MD

FINHOLT DA, AUDENAERT SM, STIRT JA, MARCELLA KL, FRIERSON HF Jr, SUDDARTH LT, RAPHAELY RC. Endotracheal tube leak pressure and tracheal lumen size in swine. Anesth Analg 1986;65:667–71.

Endotracheal tube "leak" is often estimated in children to judge the fit of uncuffed endotracheal tubes within the trachea. Twenty-five swine were intubated with uncuffed tracheal tubes to determine whether a more sensitive measurement of leaks could be devised and whether leak pressure estimates fit between tracheal tube and trachea. We compared leak pressure measurement using a stethoscope and aneroid manometer with a technique using a microphone, pressure transducer, and recorder, and found no differences between the two methods. The tracheas were then removed and slides prepared of tracheal cross-sectional specimens. Regression analysis revealed a linear relationship between tracheal lumen size and tracheal tube size for both low leak pressure ($y = -0.4 + 0.79x$, $r = 0.88$, $P < 0.05$) and high leak pressure ($y = -2.9 + 0.71x$, $r = 0.92$, $P < 0.05$) groups. We conclude that leak testing with a stethoscope and aneroid manometer is sensitive and accurate, and that tracheal tube leak pressure accurately portrays fit between tube and trachea.

Key Words: INTUBATION—tracheal. EQUIPMENT, TUBES—tracheal.

The narrowest portion of a child's airway is at the cricoid ring (1). The thin mucosal and submucosal layers surrounded by a rigid ring make this region particularly susceptible to ischemic injury from endotracheal tube compression.

Uncuffed endotracheal tubes are commonly used in children in an attempt to decrease the potential for pressure-induced ischemic injury. However, uncuffed tubes may increase the potential for aspiration and lead to erratic delivery of preset tidal volume during mechanical ventilation. Furthermore pressure-induced tracheal injury is still possible if tight-fitting, uncuffed tubes are used (2–4). Thus a variety of formulas and techniques have been used in an attempt to find the endotracheal tube size that minimizes both pressure-induced tracheal injury and aspiration potential or variable ventilation (5–9).

One such technique is the leak test. In its simplest form, the leak test involves connecting a ventilation bag to the endotracheal tube, compressing the bag, and listening for an audible escape of air (leak) around the tracheal tube and out of the mouth. To quantify the leak test, a pressure manometer may be added to the ventilation circuit and a stethoscope placed over the trachea to detect air leak. Leak pressure is defined as the airway pressure needed to generate an audible escape of gas from between the tracheal tube and trachea. An intuitive assumption then follows: high leak pressures indicate tight-fitting tracheal tubes and low leak pressures, loose-fitting tubes.

We undertook this study for two purposes: 1) to determine whether a more sensitive, precise, noninvasive method could be devised to measure leak pressure, and 2) to determine whether leak pressure predicts fit between endotracheal tube and trachea.

Methods and Materials

We divided the study into two phases. In phase 1, leak pressure detection, we sedated 25 swine (1.1–7.5

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Address correspondence to Dr. Finholt, Department of Anesthesia, University of Cincinnati Medical Center, 231 Bethesda Avenue (ML 531), Cincinnati, OH 45267.

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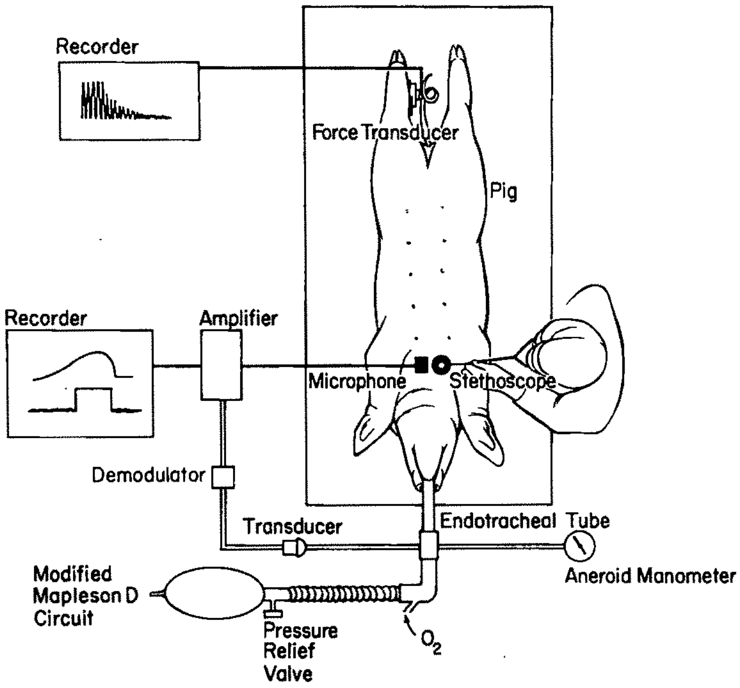

Figure 1. Schematic of experimental setup. Pigs were placed supine with the head and neck in a U-shaped harness (not shown) to ensure consistent head position.

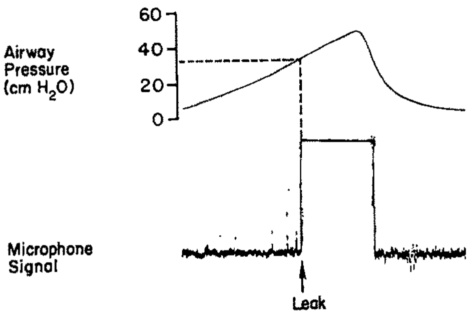

Figure 2. Sample recording from the alternate technique (microphone/transducer/recorder) for leak pressure measurement. The leak pressure is that pressure at which the microphone signal intercepts the airway pressure curve.

kg) with ketamine, 10 mg/kg intramuscularly, and attached a force transducer (Grass model FT-10) to a hind foot to monitor twitch tension in response to a supramaximal peroneal nerve stimulation of 0.15-msec duration at 0.15 Hz, delivered via two 25-gauge subcutaneously placed needles. A strip chart recorder (Gould 220 series) run at 5 mm/min was used to record the force-transducer measurements. We then administered thiamylal, 4 mg/kg, and pancuronium, 1 mg/kg intravenously. When twitch height decreased to less than 5% of control, the pigs were intubated, with the endotracheal tube placed 3 cm past the easily detectable cricoid ring. The swine were ventilated with 100% O_2 using a modified Mapleson D breathing circuit and placed supine in a U-shaped harness to ensure consistent head position. We used two methods simultaneously for leak pressure measurement (Fig. 1). In the standard method, tracheal air leak was detected with a stethoscope placed gently over the trachea, while airway pressure was monitored with an aneroid manometer connected to the breathing circuit with low compliance tubing. In the alternate method, tracheal air leak was detected with a high impedance, insulated microphone (Realistic 33-1056A) placed over the trachea, while airway pressure was monitored with a differential pressure transducer (Validyne M145-1-87) and carrier demodulator (Validyne CD15-871, 0–1 kHz) connected to the breathing circuit with low compliance tubing. Microphone and transducer signals were amplified (Hewlett–Packard 8821A medium gain amplifier, 0–15 kHz) and recorded simultaneously (Hewlett–Packard 7700 thermal recording system with model 356-100CW recorder). Once the aneroid manometer (Bourdon type pressure gauge) and strip chart recorder were calibrated, fresh gas flow was set at 5 L/min, the pressure-relief valve on the breathing circuit was closed, and recording was begun. One examiner recorded the leak pressure by noting the aneroid manometer pressure at which the first audible air leak was heard with the stethoscope. A second examiner ensured that the microphone signal gave a steady baseline and that airway pressure and leak pressure were adequately recorded (Fig. 2). Measurements were done in triplicate and averaged. The animals were then reintubated, when possible, with progressively larger tracheal tubes until we obtained a series of tracheal tubes giving leak pressures

Table 1. Comparison of Standard (Stethoscope/Manometer) with Alternate (Microphone/Transducer/Recorder) Methods of Leak Pressure Measurement

		Leak pressure measurement[a]	
Leak pressure subgroup	*n*	Standard method	Alternate method
Low pressure	22	13.2 ± 0.5	12.5 ± 0.6
High pressure	20	31.6 ± 1.2	31.3 ± 1.4
All measurements	42	21.9 ± 1.8	21.5 ± 1.9

All measurements express mean ± SEM.
[a] cm H_2O

from less than 10 cm H_2O to greater than 60 cm H_2O in each animal. Because of variability in tracheal size and configuration, we were able to intubate some pigs (9 total) with only one tube and some pigs with as many as three tubes (2 total) before leak pressure exceeded 60 cm H_2O. Twitch height remained less than 5% of control during the entire experiment. At the conclusion of our measurements, the strip chart recordings were reviewed to determine leak pressure as measured by the alternate method.

In phase 2, tracheal lumen size was measured. At the conclusion of leak pressure measurement, all 25 swine, as well as 6 unintubated control swine, were sacrificed, and the tracheas were removed and preserved in 10% formalin. After 72 hr of fixation, sections of the tracheas were obtained 2 cm distal to the cricoid ring and stained with hematoxylin and eosin. A pathologist, naive to the experiment, measured anterior–posterior and lateral tracheal lumen diameters using an oculomicrometer. Tracheal lumen areas were estimated using a standard formula for an ellipse: area = $\pi(AB)/4$. Control and experimental tracheas were graded (0, none to mild; 1, moderate to severe) for edema and cellular infiltration. One pig was removed from the study because of artifactual destruction of the tracheal specimen during slide preparation.

Analysis of Data

For phase 1, to determine whether there was a difference in leak pressure measurement as measured by the two methods, we used a paired *t*-test to compare data for all measurements. In addition, to determine whether magnitude of leak pressure affected the sensitivity of leak detection, we compared data for two leak pressure subgroups: low leak pressure (10–19 cm H_2O) and high leak pressure (20–60 cm H_2O).

For phase 2, differences in edema and cellular infiltration were assessed by Fisher's exact test to compare control (nonintubated) and experimental (intubated) tracheas, and to compare tracheas intubated twice or less with those intubated more than twice.

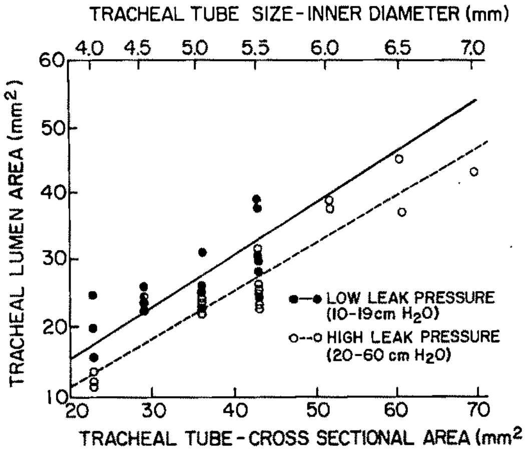

Figure 3. Graph depicting the relationship between tracheal lumen area (LA) and tracheal tube cross-sectional area (TA). The regression equation for the low leak pressure group is LA = −0.4 + 0.79 (TA), $r = 0.88$, and for the high leak pressure group is LA = −2.9 + 0.71 (TA), $r = 0.92$.

The data were again divided into two groups, low leak pressure (10–19 cm H_2O) and high leak pressure (20–60 cm H_2O), as determined using our standard method of leak pressure detection. We used regression analysis to assess the relationship between tracheal lumen area and endotracheal tube size for each leak pressure group. To test for differences between leak pressure groups, we performed an analysis of covariance. The dependent variable was tracheal lumen area and the covariant was tracheal tube cross-sectional area. In phase 1 and phase 2 we considered differences statistically significant if $P < 0.05$.

Results

Data from phase 1 is given in Table 1, which compares leak pressures as obtained by the standard (stethoscope/manometer) method and the alternate (microphone/transducer/recorder) method. No significant difference was found between the methods across all measurements, and at low or high leak pressures.

Data from phase 2 showed no difference between control and experimental tracheas when reviewed for edema and cellular infiltration. We also detected no difference in those animals intubated twice or less with those intubated more than two times.

Regression analysis demonstrated the significant linear relationship between tracheal lumen area and tracheal tube size for both the low leak pressure ($y = -0.4 + 0.79x$, $r = 0.88$) and high leak pressure groups ($y = -2.9 + 0.71x$, $r = 0.92$) (Fig. 3). Analysis of covariance revealed the regression lines for the two groups are significantly different, but have nearly identical slopes.

Discussion

Traditionally, an uncuffed endotracheal tube is said to be the correct size for a child if "a little leak" is heard with positive pressure ventilation (4). Patient conditions under which leak testing is done, method of leak detection, and estimation of degree of leak have remained nebulous.

A previous study demonstrated the need for consistent head position and stable degree of neuromuscular blockade in developing a more rigorous protocol for leak pressure measurement (10). To ensure consistent head position, we used a harness, holding each pig's head in an identical neutral position. Stable neuromuscular blockade was maintained by administering a supramaximal dose of pancuronium, resulting in $> 95\%$ twitch height depression throughout the experiments.

In the first phase of this study, we had no difficulty detecting leak around the tracheal tube with either detection method. As demonstrated in Figure 2, an accurate and reproducible recording of leak pressure can be made using the alternate method. However, we found no differences in measurement. Thus the alternate method, a highly sensitive technique for leak detection and precise measurement of airway pressure, confirmed the accuracy and utility of using a stethoscope and aneroid manometer for leak testing.

After verifying the accuracy of our standard method of leak testing, we investigated the assumption that leak pressure gives an estimate of fit between tracheal tube and trachea. In phase 2 we confirmed this assumption by demonstrating a linear relationship between tracheal lumen size and tracheal tube size for a given leak pressure (Fig. 3). Thus in two pigs with identical leak pressures, the pig intubated with a larger endotracheal tube naturally has the larger tracheal lumen. Conversely, the regression lines in Figure 3 show that in two pigs intubated with a 5.5-mm inner diameter tracheal tube, the pig with a leak pressure less than 20 cm H_2O will have a larger tracheal lumen area (approximately 33 mm^2) than the pig with a leak pressure of 40 cm H_2O (approximately 27 mm^2). And, since the slopes of these lines are not significantly different, this relationship will hold true regardless of tracheal tube size.

This phenomenon suggests the clinical utility of leak testing. For example, one may intubate a child with croup and measure initial leak pressure at 40 cm H_2O. Two days later, with the same endotracheal tube in place, leak testing reveals a leak pressure of 20 cm H_2O. If both measurements were done under the same testing conditions, one can assume that tracheal lumen size has increased and that extubation may be safely accomplished. Conversely, if a long-term intubation patient develops increasing leak pressures, and therefore decreasing lumen size, concern must arise regarding development of tracheal edema.

Is it legitimate to apply this concept in children when we obtained the data in swine? We believe so. The cricoid ring is not the narrowest portion of a pig's airway. The pig cricoid ring is elliptical, with a long anterior–posterior diameter and narrow lateral diameter. Sealing the trachea with an uncuffed endotracheal tube, as one does in a child, is not feasible in this region. Thus we chose a region of the pig trachea 2–3 cm below the cricoid ring that maintains a relatively constant cylindrical shape and diameter. Due to a sharp anterior turn of the posterior portion of the cricoid cartilage, we could detect the cricoid region easily during intubation, which enabled us to place the tube tip quite precisely 3 cm past the cricoid cartilage. Sections taken 2 cm distal to the cartilage represented the area where air escaped from the tube tip and Murphy eye. Although preservation with 10% formalin may alter tracheal tissue dimensions, each trachea would be affected similarly. Thus the linear relationshp between tube size and trachea size should not be changed by preservation. Therefore we think our study adequately mimicked the anatomic considerations of performing a leak test in a child.

In summary, we have shown that tracheal tube leak pressure can be measured accurately using a simple stethoscope/aneroid manometer system. We have also demonstrated that leak pressure testing, when done under controlled conditions, gives an excellent indication of fit between tracheal tube and trachea. Thus leak testing provides objective evidence of differences in tracheal lumen size and may be of direct clinical benefit.

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Technical Communication

The Partial Pressure of Isoflurane or Halothane Does Not Affect Their Solubility in Blood:

Inhaled Anesthetics Obey Henry's Law

Cara M. Coburn and Edmond I. Eger II, MD

Using nuclear magnetic resonance, Wyrwicz et al. studied the washin and elimination of halothane and isoflurane in the brains of rabbits (1,2). They found that the rate of cerebral elimination of halothane was slower than the rate previously determined (3), and was also slower than the rate that would be predicted from data on solubility and cerebral blood flow (4).

One explanation for the finding of Wyrwicz et al. is that the solubility (solvent/gas partition coefficient) of halothane and isoflurane in blood is higher than that reported (5–7). Most studies of solubility have applied partial pressures at approximately 1 MAC. Such studies may underestimate solubility if saturable binding sites are present at the lower partial pressures that exist during the elimination of anesthetics. The presence of binding sites in blood and muscle has been demonstrated for xenon (8) and cyclopropane (9,10). If there are binding sites in blood for halothane and isoflurane, anesthetic solubility might be relatively greater at the lower partial pressures obtained during elimination. We have tested this possibility in the present report.

Methods

With the approval of the University of California Committee on Human Research, we obtained 30 ml of venous blood from 17 fasting patients immediately before anesthesia. The blood from each patient was divided into two equal samples, one of which was equilibrated with a partial pressure of isoflurane or halothane at approximately 1 MAC, the other with a partial pressure of approximately 0.01 MAC. The same anesthetic was used for both samples drawn from a given patient. All solubilities were measured at 37°C, using a technique previously applied in our laboratory (6,11). The solubilities of these agents were also determined in normal saline at similar partial pressures.

The reader is referred to the above-mentioned reports for details of the method for measuring solubilities. Briefly, the method consists of tonometry of anesthetic between gas and solvent (e.g., blood) phases, and measurement (using gas chromatography) of the concentration of anesthetic in the gas phase. An aliquot of the solvent is transferred anaerobically to a large, closed flask and the anesthetic extracted into the gas phase of the flask. The anesthetic concentration in this gas phase is analyzed and the concentration originally present in the solvent phase determined from that concentration and the volumes of the gas and solvent phases. A small correction for the anesthetic retained by the solvent is included in this calculation. The partition coefficient equals the concentration in the solvent phase divided by the concentration in the gas phase at the end of the tonometry.

We compared the results at high vs low concentrations of both agents using both paired and unpaired *t*-tests. Unpaired tests were applied to the results for saline. Unpaired tests also were used to analyze the results for the total data for blood solubility of isoflurane because solubility determinations were not obtained at both the high and low concentrations for every pair of samples (occasional samples were lost during analysis). Paired analysis was performed for

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Address correspondence to Dr. Eger, Department of Anesthesia, 513 Parnassus Avenue, Room 1386 HSE, University of California, San Francisco, San Francisco, CA 94143.

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Table 1. Partition Coefficients for Isoflurane and Halothane at 1 MAC and 0.01 MAC

	Saline		Blood	
	High concentration	Low concentration	High concentration	Low concentration
Isoflurane				
n	8	8	10	9
Concentration (vol %)	1.10 ± 0.04	0.0118 ± 0.0004	1.01 ± 0.04	0.0111 ± 0.0004
Hemoglobin (g/dl)	—	—	13.8 ± 1.9	
Partition coefficient	0.54 ± 0.02	0.53 ± 0.03	1.51 ± 0.09	1.56 ± 0.08
Halothane				
n	8	6	9	9
Concentration (vol %)	0.60 ± 0.15	0.0057 ± 0.0018	0.50 ± 0.09	0.0052 ± 0.003
Hemoglobin (g/dl)	—	—	13.8 ± 1.9	—
Partition coefficient	0.54 ± 0.02	0.53 ± 0.03	1.51 ± 0.09	1.56 ± 0.08

All values are mean ± SD.

the samples for which both determinations were completed. We considered $P < 0.05$ statistically significant. All values obtained were mean ± SD.

Results

We found no significant difference in the solubility of halothane or isoflurane in blood or saline at high and low partial pressures (Table 1).

Discussion

The values we obtained for solubility in normal saline are comparable to those determined by others, although ours averaged slightly lower. Our value of 0.54 ± 0.02 for isoflurane at a partial pressure associated with 1 MAC did not differ from the value of 0.55 ± 0.04 obtained by Renzi and Waud in Krebs solution (12), and was only slightly lower than that of 0.59 ± 0.01 found by Lerman et al. in saline (11). Similarly, our value of 0.77 ± 0.04 for halothane in saline compared well with data found by Lerman et al. and Renzi and Waud—0.83 ± 0.02 and 0.75 ± 0.08, respectively (11,12).

The values determined for solubility in blood are slightly greater than, but within the range of, values obtained by others (5–7). Our value for isoflurane, 1.51 ± 0.09, is close to those reported by Cromwell et al. (5) and Eger et al. (6), 1.43 ± 0.02 and 1.46 ± 0.09, respectively. Similarly, our value for halothane, 2.62 ± 0.27, is consistent with the value of 2.50 ± 0.13 found by Cowles et al. (7) and with the value of 2.54 ± 0.18 determined by Eger et al. (6).

Over the range (at approximately 0.01–1 MAC) of anesthetic partial pressures studied in blood, we found no evidence of saturable binding sites. We conclude that Henry's law is followed in this range of partial pressures. If binding sites exist, they must be saturable at much higher or lower partial pressures, or be too few in number to be detected by our analyses. We did not test the effect of partial pressures that produce deep levels of anesthesia, and thus it is possible that at such levels Henry's law would not be followed.

Our results do not explain the finding of Wyrwicz et al. of prolonged retention of isoflurane and halothane in rabbit brains. Perhaps saturable sites for these anesthetics exist in rabbit blood but not in human blood. Alternatively, the explanation for their data may be the presence of saturable binding sites in the brain. A third possibility is that there are variations in solubility within the brain, and Wyrwicz et al. were measuring washout from a part of the brain with a high affinity for anesthetic. Similarly, there may be areas of low perfusion that produce prolonged time constants. Finally, the nuclear magnetic resonance measurements made by Wyrwicz et al. may not accurately reflect events in the brain. For example, they may make no distinction between the brain and the tissues overlying it. Anesthetic elimination from these tissues may have a long time constant.

Previous data have shown an initial rapid elimination of isoflurane and halothane from the lung. The alveolar rate of washout is consistent with the magnitude of the partition coefficients we and others have obtained at anesthetizing concentrations (4,5). In addition, because we found no significant difference in the solubilities of isoflurane and halothane at high vs low concentrations, we expect a linear, semilogarithmic terminal elimination curve, which would also be consistent with previous reports.

Halothane (Fluothane) for this study was donated by Ayerst Laboratories. Isoflurane (Forane) was given by Anaquest.

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Clinical Reports

Induced Hypotension for Clipping of a Cerebral Aneurysm during Pregnancy:

A Case Report and Brief Review

Barry Newman, MBChB, FFARCS, and Arthur M. Lam, MD, FRCP(C)

The anesthetic management of pregnant patients undergoing craniotomy for clipping of cerebral aneurysms can present the anesthetist with many clinical dilemmas, one of which is the role of induced hypotension and the choice of hypotensive agents. We report here the successful management of a case of cerebral aneurysm clipping in late pregnancy, where hypotension was induced and maintained with deep isoflurane anesthesia.

Case Report

A 27-year-old hypertensive woman, gravida 1, para 1, presented in her thirty-fourth week of pregnancy with a history of sudden onset of headache while vomiting. Subsequent investigation revealed a basilar artery aneurysm. She was admitted for elective clipping of the aneurysm. Preoperatively her blood pressure was controlled with methyldopa, 500 mg/day. Clinical and laboratory investigation revealed no abnormalities. Fetal heart rate and movements were normal.

The night before surgery the patient received cimetidine, 300 mg orally, and fasted overnight. Two hours before surgery was scheduled, an intravenous infusion was commenced, and the patient received 300 mg of cimetidine and 10 mg of metoclopramide intravenously.

Prior to induction of anesthesia, the patient was placed in a left 15° tilt position, the fetal heart rate was continously monitored with a Doppler ultrasound monitor, and the patient was preoxygenated for 4 min. Fentanyl, 150 μg, lidocaine, 100 mg, thiopental, 375 mg, and succinylcholine, 120 mg, were given intravenously. Cricoid pressure was immediately applied and released after tracheal intubation and inflation of the tracheal tube cuff. Before induction, the systolic arterial pressure was 160 mm Hg; 1 min after intubation, it was 140 mm Hg. Subsequent neuromuscular blockade was maintained with a total of 14 mg of pancuronium, and anesthesia was maintained with 1.0% isoflurane and nitrous oxide in 50% oxygen.

Monitoring included an arterial and a central venous catheter, an electrocardiogram, a rectal temperature probe, and a Doppler ultrasound fetal heart monitor. Arterial gas tensions were measured intermittently. The Pa_{O_2} was above 100 mm Hg at all times, and the minute ventilation was adjusted to maintain the Pa_{CO_2} between 30 and 35 mm Hg. A catheter was inserted into the lumbar subarachnoid space for intraoperative cerebrospinal fluid drainage, and the patient was placed in the left lateral position.

During dissection and clipping of the aneurysm, blood pressure was reduced by increasing the inspired isoflurane concentration to between 1.5 and 2.0%. The response was immediate, and arterial pressure was maintained between 50 and 70 mm Hg for 40 min and the lowest mean pressure of 50 mm Hg (65/42 systolic/diastolic) was held for 15 min during application of the clip. At all other times mean arterial pressure was maintained between 80 and 105 mm Hg. An arterial blood sample drawn for gas chromatographic analysis at the end of hypotension revealed the arterial isoflurane concentration to be equivalent to an alveolar concentration of 1.2% (1).

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Address correspondence to Dr. Lam, Department of Anaesthesia, University Hospital, PO Box 5339, Postal Station A, London, Ontario, Canada N6A 5A5.

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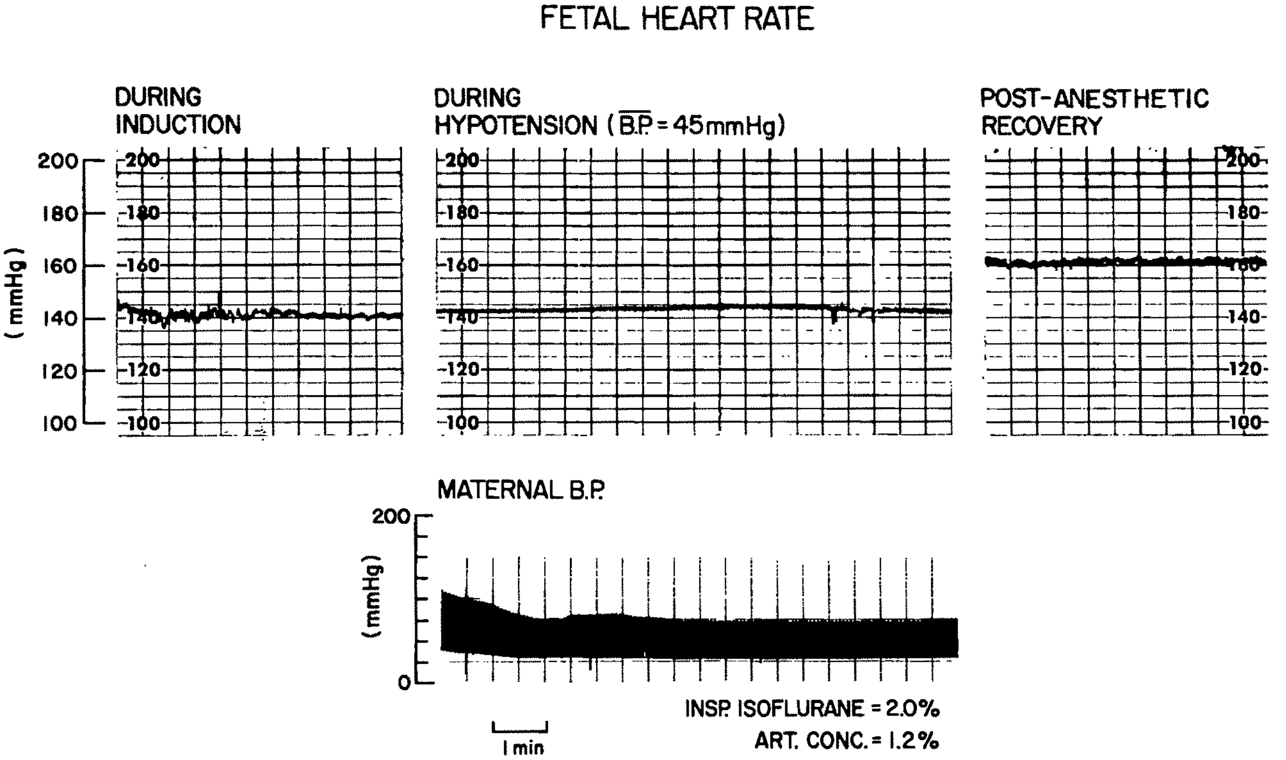

Figure 1. Fetal heart rate monitoring during the surgical procedure. Note absence of fetal heart rate changes during isoflurane-induced hypotension.

On induction of anesthesia, fetal cardiac beat-to-beat variation was immediately lost and did not return until 15 min after the patient had regained consciousness. Throughout the operation, the fetal heart rate remained between 130 and 140 beats/min. There was no change during the hypotensive period (Fig. 1).

Postoperatively the patient made a rapid and uneventful recovery. The fetal heart rate was monitored for 36 hr and no significant changes were detected. The patient was discharged from the hospital on the fifth postoperative day and was admitted to another center in spontaneous labour 3 weeks later. At 5 cm of cervical dilatation, an abrupt fetal bradycardia was detected. With the patient under general anesthesia, an emergency cesarean section was performed and a prolapse of the cord was found. The 3.5-kg infant that was delivered had a 1-min Apgar score of 5 and a 5-min score of 9. The mother tolerated the anesthetic well, made a normal postoperative recovery, and was discharged with her healthy infant.

Discussion

The incidence of subarachnoid hemorrhage caused by rupture of cerebral aneurysms is not influenced by pregnancy (2). Several recent reports have described the anesthetic management of cesarean section immediately followed by clipping of a cerebral aneurysm under the same general anesthetic (3–5). However, the ideal management of cerebral aneurysms that present during pregnancy is elective surgical occlusion followed by spontaneous vaginal delivery, if possible (6). As these aneurysms most frequently present in the third trimester of pregnancy (6), the anesthetist is faced with all the potential problems of general anesthesia in late pregnancy as well as the special problems associated with neurovascular surgery. The benefits of drugs and techniques normally used for neurosurgical procedures must be balanced against potential risks to the fetus and the mother.

Both before and at induction of anesthesia, measures must be taken to prevent aspiration of gastric contents, and also to prevent the hypertensive response to intubation, which may precipitate a subarachnoid hemorrhage. A rapid-sequence induction with preoxygenation, thiopental, succinylcholine, and cricoid pressure will serve the former requirement, but not the latter. However, a more gradual induction, including spontaneous or controlled ventilation with a face mask, may result in gastric aspiration. Our patient received cimetidine and metoclopramide preoperatively to reduce the volume and increase the pH of the gastric contents, and a rapid-sequence induction, including fentanyl and lidocaine, was used. This method prevented aspiration of gastric contents while obtunding the sympathetic response to intubation.

Recording the fetal heartbeat or ECG is currently the only practical way of monitoring fetal well-being during anesthesia. Loss of beat-to-beat variation may be an early sign of asphyxia, but may also be caused by a variety of central nervous system depressants, such as barbiturates and volatile anesthetics. In view of the latter possibility, loss of beat-to-beat variation on induction of anesthesia was anticipated in this case and not interpreted as a sign of fetal hypoxemia (7). The fetal heart rate was used as a guide throughout the anesthetic to monitor fetal well-being and particularly to determine the safe level of induced hypotension. Had the fetus developed tachycardia or bradycardia, the surgeons would have been informed and the blood pressure immediately increased.

Controlled hypotension is routinely employed to facilitate aneurysm clipping, and its use in pregnancy has been recommended (6). However, which hypotensive agent is best is far from clear, and, despite three reports on the use of sodium nitroprusside in the management of aneurysm surgery in pregnant patients (8–10), its use in pregnancy remains controversial (11). Evidence from animal studies as to whether sodium nitroprusside crosses the placenta readily is contradictory, perhaps because of species differences (11). One study in ewes suggested that acidosis and cyanide accumulation occurs to a greater degree in the fetus than in the mother (12). The fetus has less thiosulphate substrate for rhodanase detoxification of cyanide than the adult and may be particularly vulnerable to the development of cyanide toxicity from sodium nitroprusside infusion (12). Moreover, the use of sodium nitroprusside is almost always accompanied by tachycardia, which may necessitate the administration of β-blocking drugs. When given to pregnant women, β-blockers are associated with a wide variety of fetal and neonatal disturbances, such as bradycardia and hypoglycemia (13).

Trimethaphan has also been used for hypotension during pregnancy. However, the fact that trimethaphan causes reduction in both cardiac output and cerebral blood flow makes it an unsuitable agent for this purpose (14).

Isoflurane induces easily controlled and reversible hypotension associated with peripheral vasodilation and with little effect on cardiac output (15), pulmonary gas exchange (16) and cerebral blood flow in neurosurgical patients (17). Isoflurane is also a potent depressor of cerebral oxygen consumption, and this favorably influences the cerebral oxygen supply/demand balance during hypotension (17). At 1.5 MAC, isoflurane has no effect on uterine blood flow, fetal base excess, or fetal oxygenation despite a reduction in maternal blood pressure (18). In nonpregnant patients, the arterial isoflurane concentration required for induction of hypotension is approximately 1.8% (alveolar equivalent) (15). In our patient, the arterial isoflurane concentration at the end of the hypotensive period was 1.2%, possibly reflecting the reduced requirements for inhaled anesthetics during pregnancy (19). The general characteristics of isoflurane and the experience of this case suggests that isoflurane may be particularly well-suited for the induction of hypotension in pregnant patients.

Regarding the use of osmotic diuretics, in pregnant rabbits given 12.5 gm/kg mannitol, bulk flow of solution from the fetal to the maternal extracellular space has been demonstrated (20). In humans, the administration of 200 gm of mannitol to the mother shortly before delivery alters volume and concentration of solutes in the fetus, including an increase in total osmotic pressure (21). However, in the doses used in clinical practice (0.5–1.0 gm/kg), mannitol is unlikely to cause prolonged or severe fluid or electrolyte disturbances in the fetus. In the case reported here, surgical conditions did not require further brain volume reduction for adequate exposure. Had it been necessary, mannitol 0.5–1.0 gm/kg would have been infused.

Maternal hyperventilation with marked hypocapnia may reduce placental perfusion by depression of cardiac output (22) and by direct placental vasoconstriction (23). The induced alkalosis may also reduce maternal hemoglobin oxygen unloading by a left shift of the oxygen dissociation curve (22). Excessive hyperventilation should therefore be avoided in this clinical setting, particularly during induced hypotension. For these reasons we maintained maternal Pa_{CO_2} above 30 mm Hg.

In summary, we report the successful anesthetic management of a pregnant patient in the third trimester undergoing cerebral aneurysm clipping during isoflurane-induced hypotension. On the basis of this case and a review of the literature we recommend the following:

The danger of aortocaval compression should be recognized and appropriate positioning used at all times.

The induction of anesthesia in these patients should be designed to prevent pulmonary aspiration, as well as the reflex hypertension associated with tracheal intubation.

Initiation of fetal heart monitoring should be done prior to induction and maintained thereafter throughout the procedure.

Although induced hypotension may be safely employed in pregnant patients, the level of hypotension should be guided by the fetal heart rate. Isoflurane may be superior to sodium nitroprusside for this purpose.

If required, moderate doses of mannitol should be used to facilitate surgery.

Extreme hyperventilation should be avoided, particularly during hypotension.

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The Effect of High Frequency Positive Pressure Ventilation on Right and Left Ventricular Function

J. Biondi, MD, R. Hines, MD, T. Rafferty, MD, P. Rogol, MD, W. Scott, MD, and P. Barash, MD

Intermittent positive pressure ventilation (IPPV) with positive end expiratory pressure (PEEP) can cause hemodynamic dysfunction and limit tissue oxygen transport (O_2T). Studies suggest that this heart–lung interaction is a direct effect of elevated mean airway pressure which causes decreased venous return (1), increased right ventricular afterload (pulmonary vascular resistance) (2), decreased biventricular end diastolic volumes (3), altered cardiac geometry (4), altered ventricular interdependence (leftward displacement of the ventricular septum) (5), and decreased contractility (6). Alternatively, high frequency positive pressure ventilation (HFPPV) has been recommended for use in mechanically ventilated patients with profound respiratory phasic depression of cardiac function. By minimizing convective gas flow in the lung, HFPPV maintains alveolar oxygenation and functional residual capacity (FRC), at subambient transthoracic pressures, and is reported to preserve hemodynamic function (7). Experimental studies in control and acute lung injured animals have verified these physiologic effects, but the clinical data corroborating these results are limited.

This case report details the effect of HFPPV, as driving pressure (DP) is increased over a range of 20–50 psi, on right and left ventricular performance, using standard hemodynamic and thermal ejection fraction techniques. These data suggest that cardiac function declines linearly as driving pressure increases during HFPPV, and that in conditions of acute lung injury requiring DP >30 psi, HFPPV affords no cardiorespiratory advantage over IPPV.

Case Report

A 68-yr-old male was admitted to Yale–New Haven Hospital for elective coronary revascularization. Six weeks prior to admission he sustained an acute inferior wall myocardial infarction associated with a peak creatine kinase elevation of 640 units (normal 0–63 units) that was complicated by post-infarct angina. Cardiac catheterization revealed angiographically significant triple vessel disease (100% right coronary artery occlusion, 95% left anterior descending occlusion, and 90% left circumflex artery occlusion). The left ventriculogram showed inferobasilar akinesis, good anteroapical wall motion, and a left ventricular ejection fraction of 30% (normal 55% ± 10). Medications included metoprolol, 50 mg, twice daily and sublingual nitroglycerin as necessary for his anginal symptoms. The patient also had a history of chronic obstructive pulmonary and aortoocclusive disease.

Physical examination revealed an elderly male in no acute distress. Vital signs were stable: blood pressure 130/70 mm Hg, heart rate (HR) 64 beats/min, respiratory frequency 14 breaths/min, temperature 36.5°C, and body surface area 1.89 m^2. Pertinent physical findings included an increased anterior–posterior diameter of the thorax and expiratory wheezing. Cardiac examination revealed a normal S_1 and S_2 and a soft, but audible third heart sound. The apical impulse was displaced laterally. Distal pulses were normal, and the remainder of the examination was unremarkable.

Pertinent preoperative data included, at an F_{IO_2} of 0.21, an arterial pH of 7.40, a Pa_{O_2} of 68 mm Hg, a Pa_{CO_2} of 37 mm Hg, an oxygen saturation of 93%, and a HCO_3^- of 22.6 mEq/L. Pulmonary function studies showed a 1-sec forced expiratory volume (FEV_1) of 1.89 L (normal 3.34 L), a forced vital capacity (FVC) of 3.81 L (normal 4.75 L) and an FEV_1/FVC ratio of 50% (normal 70%). The maximal mid-expiratory flow rate was 0.63 L/sec (normal 0.75 L/sec). PA and lateral chest roentgenograms were notable for bilateral upper

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Address correspondence to Dr. Biondi, Department of Anesthesiology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510.

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Table 1. Hemodynamic Data during HFPPV and during IPPV

Event	Ventilation mode	Rate (F/min)	F_{IO_2}	PEEP (cm H_2O)	DP (mm Hg)	AP (mm Hg)	HR (beats/min)	MAP (mm Hg)	RAP (mm Hg)
Induction	IPPV	10	1.0	0	—	32 p	64	88	6
Post CPB	IPPV	10	1.0	0	—	46 p	85	75	10
Postop 12 hr	IPPV	10	1.0	0	—	52 p	115	68	8
Postop 15 hr	IPPV	10	1.0	20	—	60 p	110	62	11
Postop 16 hr	IPPV	10	1.0	25	—	67 p	113	57	13
Postop 17 hr	HFPPV	140	1.0	10	25	18 m	121	80	12
Postop 19 hr	HFPPV	140	0.7	10	30	24 m	117	76	11
Postop 22 hr	HFPPV	140	0.6	10	35	30 m	105	71	13
Postop 23 hr	HFPPV	140	0.6	10	40	38 m	100	68	14

Abbreviations: HFPPV, high frequency positive pressure ventilation; IPPV, intermittent positive pressure ventilation; PEEP, positive end-expiratory pressure; DP, driving pressure; AP, airway pressure; HR, heart rate; MAP, mean arterial blood pressure; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; RVEF, right ventricular ejection fraction; RVSWI, right ventricular stroke work index; LVSWI, left ventricular stroke work index; O_2TI, tissue oxygen transport index; PAPM, mean pulmonary artery pressure; Q_s/Q_t, shunt fraction, A-aO_2, alveolar-arterial oxygen difference.

lobe lucencies with bullae, flattened diaphragms, bibasilar atelectasis, and chronic interstitial fibrosis. An electrocardiogram showed an old inferior wall infarct and a right bundle branch block pattern.

After premedication and placement of radial and pulmonary artery catheters, anesthesia was induced with fentanyl (75 μg/kg) followed by pancuronium (0.1 mg/kg). Baseline hemodynamic measurements were as follows: HR 65 beats/min, mean arterial blood pressure (MAP) 80 mm Hg, right atrial pressure (RAP) 6 mm Hg, pulmonary artery pressure (PAP) 28/18 mm Hg, pulmonary capillary wedge pressure (PCWP) 16 mm Hg, and cardiac output (CO) 4.5 L/min. Ventilation was maintained via an endotracheal tube using an F_{IO_2} of 1.0 and a tidal volume of 12 ml/kg to maintain a normal pH, the pH being 7.42, the Pa_{CO_2} 38 mm Hg, and the Pa_{O_2} 347 mm Hg. Initiation of cardiopulmonary bypass (CPB) was uneventful, and a three-vessel aorto-coronary bypass grafting operation was performed without difficulty. The patient was weaned from CPB and stabilized with intravenous epinephrine (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and nitroglycerin (2 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Post-CPB arterial blood gases on an F_{IO_2} of 1.0 were pH 7.32, Pa_{CO_2} 36 mm Hg, Pa_{O_2} 280 mm Hg, Sat 99.9%, and HCO_3 21 mEq/L. Hemodynamic measurements were HR 85 beats/min, MAP 75 mm Hg, RAP 10 mm Hg, PAP 30/12 mm Hg, PCWP 12 mm Hg, and CO 3.8 L/min.

Postoperatively the patient's course was complicated by increasing arterial hypoxemia. Intermittent mandatory and controlled ventilation with PEEP (5–20 cm H_2O) were unsuccessful in improving arterial oxygenation. Further, higher levels of PEEP associated with peak inspiratory pressures of 70–80 cm H_2O produced hemodynamic instability. High frequency positive pressure ventilation was, therefore, instituted using a Healthdyne Model 303 Impulse ventilator. Inspired gas was delivered via a 1.62 mm × 8.3 cm steel cannula inserted into a 15-mm adaptor connected to the end of the endotracheal tube. High flow jet gas was humidified using 15–30 ml/hr of 0.45 normal saline, and the entrained gas source was humidified and heated (T 36°C). Ventilator settings, including a respiratory rate of 140 cycles/min and an inspiratory/expiratory ratio of 0.3, were held constant. Driving pressure (DP) was varied over a range of 15–40 psi, and F_{IO_2} (mean 0.7) was altered as necessary to maintain Pa_{O_2} at 60–80 mm Hg. PEEP was kept constant at 10 cm H_2O. Hemodynamic data (Table 1) were recorded and CO and right ventricular ejection fraction (RVEF) were calculated from diastolic washout plateaus obtained from a rapid response thermistor Swan–Ganz catheter (8). These data are considered in detail in the discussion.

HFPPV was continued for 72 hr during which the patient's alveolar gas exchange and ventilatory mechanics steadily improved. Chest radiographs before and after HFPPV showed progressive bibasilar lung expansion. Fiberoptic bronchoscopy was performed every 24 hr to assess airway hydration. IPPV was resumed as oxygenation and hemodynamic performance reached optimal levels. Mechanical ventilatory support was gradually decreased over a 10–14 day period. The patient was discharged from the hospital in satisfactory condition on the 40th postoperative day.

Discussion

Theoretical considerations of HFPPV focus on the use of small tidal volumes ($V_T <$ dead space) at high frequencies to achieve ventilation without circulatory depression or pulmonary barotrauma.

At low driving pressures (10–25 psi), low volume

Table 1. *(continued)*

PAPM (mm Hg)	PCWP (mm Hg)	CI ($L \cdot min^{-1} \cdot m^{-2}$)	RVEF (%)	RVSWI ($g \cdot min^{-1} \cdot m^{-2}$)	LVSWI ($g \cdot min^{-1} \cdot m^{-2}$)	PaO_2 (mm Hg)	O_2TI ($ml \cdot min^{-1} \cdot m^{-2}$)	Q_s/Q_t (%)	$A\text{-}aO_2$ (mm Hg)
22	16	2.41	—	8	37	347	705	18	328
18	12	2.01	—	2	21	280	473	24	398
22	14	2.59	29	6	15	50	511	56	618
25	16	2.23	24	5	13	58	469	53	607
31	17	1.67	18	3	10	61	338	51	601
26	18	5.20	36	8	41	96	1169	33	572
30	15	3.20	29	7	22	71	707	29	388
35	19	2.80	24	7	20	69	613	28	319
42	22	2.43	21	9	16	73	542	25	314

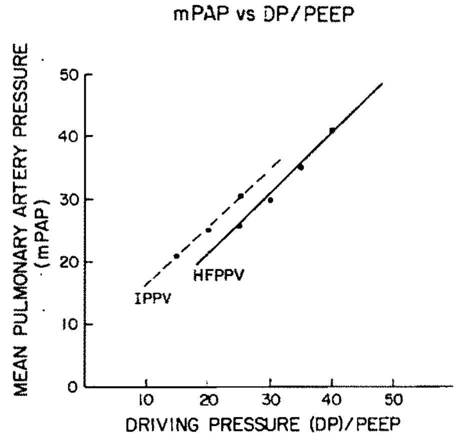

Figure 1. Mean pulmonary artery pressure increases linearly as a function of driving pressure.

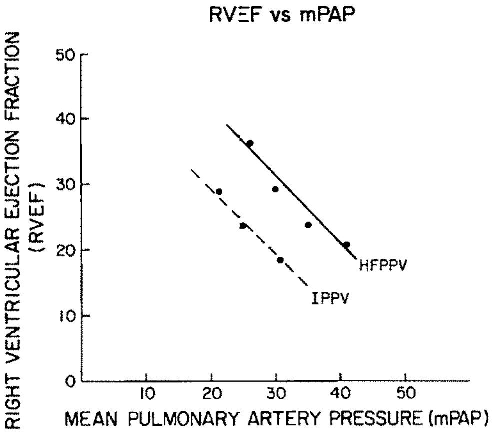

Figure 2. Right ventricular ejection fraction decreases linearly as a function of driving pressure.

(3–5 ml/kg) and high frequency (>75 beats/min) ventilation results in low peak and mean airway pressures. At low transpulmonary and transthoracic pressures, right and left ventricular preload remains normal and pulmonary vascular resistance is not elevated. Oxygen transport (O_2T) remains normal and may be improved in the absence of cyclical decreases in cardiac output (9). Improvements in arterial oxygenation stem from more homogenous alveolar gas mixing throughout the lung zones 1–3 and the subsequent conversion of low ventilation/perfusion ($\dot{V}/\dot{Q}$) sub-units to more normal states. Further oxygen transport, at the level of the alveolar capillary membrane, may be facilitated by augmented molecular diffusion. Studies have suggested that among patients with significant $\dot{V}/\dot{Q}$ imbalance, 65–80% benefit by these mechanisms from the institution of HFPPV (7).

At high driving pressures (25–50 psi), HFPPV may similarly facilitate oxygenation in patients with acute lung injury. High critical opening airway pressures and significant right to left intrapulmonary shunting ($\dot{Q}_s/\dot{Q}_t$), however, require positive pressure mechanical ventilation at high FRC. During HFPPV, minute ventilation is a direct function of DP with jet gas flow and total lung volume increasing in a linear relationship (10). As DP increases so too does airway pressure. This translates into increased right ventricular afterload as pulmonary capillaries are mechanically compressed at increased lung volumes. In our patient mean pulmonary artery pressure (PAPM) increased as a linear function of DP (Fig. 1). Right ventricular function as determined by thermal RVEF further deteriorated with increased DP (right ventricular afterload) (Fig. 2). Cardiac index, which improved dramatically from 1.67 $L \cdot min^{-1} \cdot m^{-2}$ to 5.2 $L \cdot min^{-1} \cdot m^{-2}$ with the institution of HFPPV at DP 25 psi, decreased with both HFPPV and IPPV as mean airway pressure increased in the absence of concurrent intervention or changes in right and left ventricular preload. This initial marked improvement in cardiac index probably represented a rebound effect related to both the central redistribution of blood volume and the decrease in PVRI, which followed the decrease in airway pressure during this transition.

This case study supports the utility of HFPPV when gas exchange is accomplished at low driving pressures that can maintain transthoracic and transpulmonary pressures at subambient levels. During these conditions HFPPV may maintain cardiovascular stability and minimize the risk of pulmonary barotrauma. At high driving pressures, however, cardiac function deteriorates with increased right ventricular afterload, and this parallels the hemodynamic effects seen with IPPV. We suggest that HFPPV may afford no greater hemodynamic stability than conventional IPPV in conditions of acute lung injury in which high pressure, HFPPV is necessary to maintain FRC and adequate alveolar ventilation.

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Controlled Hypotension for Orthognathic Surgery

Glenn A. Fromme, MD, Ronald A. MacKenzie, DO, Allan B. Gould Jr, MD,
Bruce A. Lund, DDS, and Kenneth P. Offord, MS

Hypotensive anesthesia has three potential benefits: 1) reduced blood loss with a consequent reduction in risks associated with blood transfusion; 2) improved quality (dryness) of the operative field, potentially allowing more accurate dissection and improved surgical results; and 3) reduced operative time. For the most part, studies of hypotensive anesthesia have shown a reduced blood loss that has been statistically significant (1–3). Nonetheless, the clinical importance of a small but statistically significant reduction in blood loss remains controversial when weighed against the added possible risk and expense of inducing hypotension. Reductions in operative time have also been statistically significant in some (2,4), but not all studies (3,5).

Improvement of the quality of the operative field has been studied less extensively. Several authors have concluded that the quality of the operative field is improved, but give little objective evidence to support this conclusion (4,6). One report claims that postoperative swelling was reduced and the quality of surgical results was improved based on subjective anecdotal observations without matched controls (4). A few studies do suggest some measurable improvement in the surgical field. Grundy et al. (5) reported on 24 patients undergoing Harrington rod operations, 13 of which were performed with controlled hypotension. The surgeons were able to identify correctly whether or not controlled hypotension was employed in 20 out of the 24 cases.

Chan et al. (7) reported on 21 patients undergoing orthognathic procedures, 11 of which were performed with controlled hypotension to a mean arterial pressure of 70 mm Hg. At the end of each case, the surgeons rated the quality of the surgical field on a scale of 1–3. The authors were unable to demonstrate any statistically significant differences between the control and experimental groups in measured blood loss, quality of the surgical field, or operative time. However, these authors did find statistically significant differences if they redefined their experimental group as patients whose mean blood pressure intraoperatively was less than 80% of the mean blood pressure recorded on the hospital chart. In addition, no mention was made as to whether the surgeons were blinded to the anesthetic technique used.

Our study was designed to determine whether induction of hypotension alone resulted in a statistically significant difference in the surgeon's observation of the dryness of the operative field if the surgeon was effectively blinded from the anesthetic technique used.

Methods

We studied 56 ASA class I patients requiring orthognathic surgery. All operations involved multiple osteotomies with repositioning of bony segments in both mandible and maxilla. The study was approved by the institution's human studies committee and all patients gave informed consent. Anesthesia was induced with 4–6 mg/kg sodium thiopental. All patients were pretreated with metocurine, 2 mg, and received 1.5 mg/kg succinylcholine to facilitate nasotracheal intubation. Patients received intravenous fluids consisting of lactated Ringer's with 5% dextrose at standard maintenance rates. A radial artery catheter was inserted to measure blood pressure continuously and to monitor arterial blood gas tensions. Patients were mechanically ventilated to maintain $Pa{CO_2}$ between 35 and 45 mm Hg and a $Pa{O_2}$ above 100 mm Hg. For the operation, patients were placed in the supine position with a 15° head elevation. All operations were performed by the same surgeon. Patients were randomly assigned to three groups. Group 1 patients were anesthetized with enflurane and 66% nitrous oxide in oxygen, and were kept normotensive (MAP 90–100 mm Hg). Group 2 patients received morphine

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Address correspondence to Dr. Fromme, Department of Anesthesiology, Mayo Clinic and Mayo Foundation, Rochester, MN 55905.

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Table 1. Surgeons' Scale for Quality of Surgical Field

5	Massive uncontrollable bleeding
4	Bleeding, heavy but controllable, that significantly interfered with dissection
3	Moderate bleeding that moderately compromised surgical dissection
2	Moderate bleeding, a nuisance but without interference with accurate dissection
1	Bleeding, so mild it was not even a surgical nuisance
0	No bleeding, virtually bloodless field

sulphate intravenously in 2–4 mg increments up to 24 mg, plus 66% nitrous oxide in oxygen as well as enflurane in a concentration sufficient to maintain MAP in the 75–85 mm Hg range. Group 3 patients received enflurane, 66% nitrous oxide in oxygen, and an intravenous infusion of sodium nitroprusside sufficient to maintain MAP at 55–60 mm Hg. The surgical team was blinded regarding which technique was in use and was asked to evaluate the dryness of the surgical field at half-hour intervals based on a numerical scale of 0–5 (Table 1). The values were averaged for each patient and the means ± SD for each group were compared using analysis of variance, *t*-test, and the Wilcoxon rank sum test. Blood loss was determined using volumetric and gravimetric methods. These data were also examined by the same statistical analyses.

Results

There were no statistically significant differences between the groups with respect to age, height, weight, duration of surgery, or amount of transfusions (Table 2). The mean quality of the surgical field (±SD) was 1.89 ± 0.52, 1.92 ± 0.30, and 1.90 ± 0.37 for groups 1, 2, and 3, respectively (Table 3). The differences were not statistically significant. Mean measure blood loss was 965.28 ± 530.97, 800.71 ± 270.86, and 827.62 ± 350.48 for groups 1, 2, and 3, respectively (Table 4). Differences here were also not statistically significant. The duration of hypotension induced with nitroprusside in this study averaged 6.55 ± 1.78 hr. No complications resulted from anesthesia or induced hypotension in any of the groups.

Discussion

The amount of blood lost during a surgical procedure depends on many factors. Traditionally, arterial blood pressure has been regarded as one of the most important of these, but many researchers question this assumption.

Most anesthesiologists and surgeons believe that reducing blood pressure reduces blood loss. Such a reduction has been shown to be true for many operations (1–3), and has been assumed to be true for others. But can this assumption truly be made? We feel it is unsafe to assume that the response of all vascular beds to hypotension and surgical trauma is identical, because it is well known that blood flow to each tissue is governed by neural, hormonal, and local factors (8). The few studies reported in the field of orthognathic surgery have been poorly done and inconclusive.

Another unresolved issue is just how much of a saving in blood loss is necessary to justify the risk and expense of inducing hypotension. The same question exists with respect to improvements in the surgical field. A drier field resulting from induced hypotension may allow more accurate dissection and better surgical results (for example, in plastic operations). In addition, morbidity may be reduced by lessening the risk of unintentional surgical trauma to structures that should be avoided, such as certain vessels and nerve roots. Unfortunately, all of these factors are difficult to measure objectively.

In orthognathic surgery, multiple osteotomies are made in the maxilla and mandible, permitting repositioning of segments to correct asymmetric alignment of the teeth and to ameliorate facial proportions. Because calculations are made and osteotomies performed based on careful measurements, it is easy to envision how a dry field can help. If a clinically significant difference exists, surgeons ought to be able to recognize it from the appearance of the field.

In this study, the surgeons were not informed which technique was in use or what the blood pressure was. Their unbiased evaluations of the surgical field demonstrated no significant differences between the three groups (Fig. 1). Similarly, our results show no significant differences in measured blood loss. However, a close look at the data (Fig. 2) reveals three patients in group 1 in whom measured blood loss was greater than in any patient in the other groups.

This greater blood loss may be due to chance, or these patients may represent a subset of patients who, because of differences in vascular reactivity, have a tendency to bleed excessively. We can speculate that the reason these outlying values are not seen in groups 2 and 3 is that in the hypotensive groups this type of patient has responded to the reduction in blood pressure and blended in with the rest of the group. Because these patients are such a small percentage in the study population, they do not change the mean

Table 2. Patient Characteristics Compared across the Three Treatment Groups

	Group 1 (enflurane only; MAP 90–100 mm Hg; *n* = 18)	Group 2 (enflurane plus morphine; MAP 75–85 mm Hg; *n* = 17)	Group 3 (enflurane plus nitroprusside; MAP 55–60 mm Hg; *n* = 21)
Age (yr)	21.5 ± 3.9	25.4 ± 9.0	23.5 ± 4.4
Height (cm)	169.9 ± 8.3	167.5 ± 9.3	167.1 ± 9.6
Weight (kg)	63.4 ± 11.2	65.2 ± 9.4	65.1 ± 10.7
Duration of Surgery (hr)	7.8 ± 1.6	7.6 ± 1.2	7.5 ± 2.1
Number of Transfusions	0.8 ± 1.0	0.5 ± 0.7	0.4 ± 0.7
Percent without Transfusions	44.4 ± 11.7	35.3 ± 11.6	33.3 ± 10.3

All values are mean ± SD. No statistically significant differences were detected by analysis of variance or Wilcoxon rank sum tests. $P < 0.05$ was considered significant.

Table 3. Quality of the Surgical Field as Assessed by the Surgical Team

	Mean ± SD	Low	High	Significance
Group 1	1.89 ± 0.52	1.11	2.88	N.S.[a]
Group 2	1.92 ± 0.30	1.37	2.53	N.S.[a]
Group 3	1.90 ± 0.37	1.17	2.58	N.S.[a]

[a] N.S., not significantly different from other groups by *t*-test, analysis of variance, and Wilcoxon rank sum test.

Table 4. Measured Blood Loss

	Mean ± SD (ml)	Low (ml)	High (ml)	Significance
Group 1	965.28 ± 530.97	292	2100	NS[a]
Group 2	800.71 ± 270.86	397	1260	NS[a]
Group 3	827.62 ± 350.48	293	1478	NS[a]

[a] NS, Not significantly different from other two groups by *t*-test, analysis of variance, and Wilcoxon rank sum test.

blood loss for the group enough to render group 1 significantly different from either of the two hypotensive groups. In terms of blood loss, only these few patients in this study group would actually benefit from induced hypotension, which does not support its routine use but could rationalize use of induced hypotension for that particular patient who appears to bleed excessively.

Differences in vascular reactivity could also explain why our results differ from those of others (2). We have speculated that such differences might exist even in a fairly homogenous (young and healthy) population, such as the one we studied. The percentage of patients exhibiting this phenomenon may be much larger in certain populations, such as elderly patients who undergo total hip arthroplasty, and statistically significant differences might be more likely to occur.

Surprisingly, we found only a modest correlation between the quality of the surgical field and the measured blood loss ($r = 0.21$), with a great deal of scatter (Fig. 3). In other words, there were patients who had a large blood loss but good quality of the surgical field as well as patients with a small blood loss and poor quality of the surgical field. We feel these results argue against previous claims that an improvement in the quality of the surgical field necessarily follows from a statistically significant reduction in measured blood loss. Thus, whereas our data for measured blood loss suggest a rare patient who might benefit from induced hypotension, our data on quality of the surgical field do not.

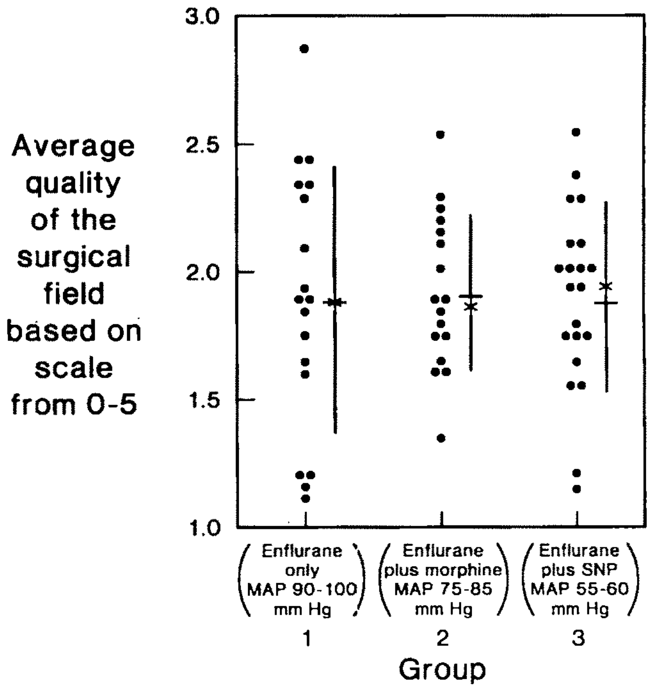

Figure 1. Scattergram showing average quality of surgical field for each group as assessed by the surgical team. Horizontal dash represents mean value for group. Asterisk represents median value for group. Vertical line represents standard deviation.

In conclusion, although nitroprusside can be safely used in healthy patients to induce hypotension to a MAP of 55–60 mm Hg for up to 7 hr, our data do not support the routine use of this technique in orthognathic surgery.

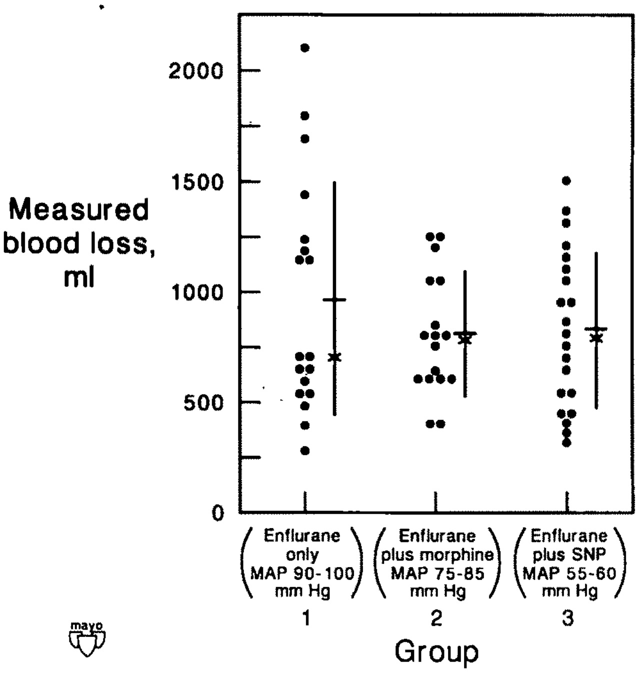

Figure 2. Scattergram showing measured blood loss for each group. Horizontal dash represents mean value for group. Asterisk represents median value for group. Vertical line represents standard deviation.

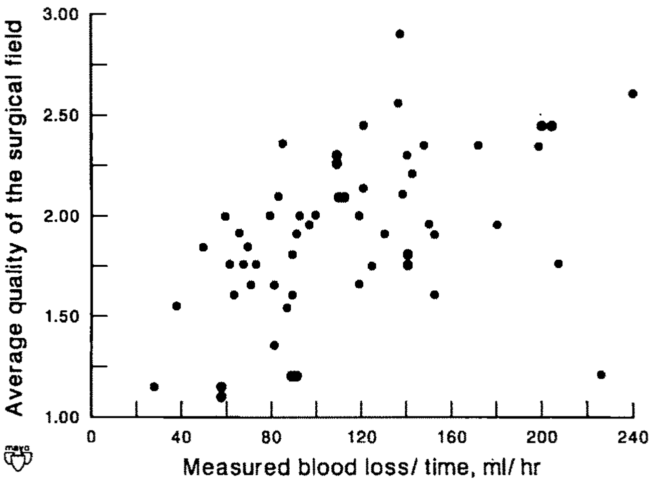

Figure 3. Graph showing relationship between measured blood loss per unit of time and quality of the surgical field.

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Local and Spinal Anesthesia for Cesarean Section in a Patient with Myotonic Dystrophy

Doris K. Cope, MD, and John N. Miller, MD

Myotonic dystrophy is the most common adult form of muscular dystrophy. However, unlike other muscular dystrophies, it is accompanied by myotonia, a delayed relaxation of muscles after contraction, and by widespread, multisystem pathology. Classical features of the disease include myopathic facies; dysarthria; presenile cataracts; wasting and weakness of facial, sternocleidomastoid and distal limb muscles; frontal baldness; and primary gonadal atrophy (1,2,3).

Although ovarian atrophy is a common feature of the disease, the data concerning associated infertility are conflicting (3,4,5). However, exacerbation of symptoms during pregnancy is common and has been linked to increases in progesterone levels (4,6). Because myotonic dystrophy affects smooth muscle as well as cardiac and skeletal muscle, it is not unusual to find an increased incidence of uterine inertia, retained placenta, and postpartum hemorrhage. Other obstetrical complications can include polyhydraminos, premature onset of labor, breech presentation, and ineffective uterine contractions in labor that often necessitate cesarean section (1–8).

Complications of inhalation anesthesia, muscle relaxation, and regional anesthesia have been reported in parturients with myotonic dystrophy. However, we found no case reports describing the effects of spinal anesthesia combined with local anesthetic applied directly on the uterine muscle during cesarean section. This case report describes some complications of delivery by cesarean section in a myotonic parturient and suggests an alternative to general anesthesia in such cases.

Case Report

A 24-yr-old gravida 2, para 1 was admitted to the hospital in labor with spontaneous rupture of membranes at 36 weeks gestation as determined by ultrasound and dates. Her earlier pregnancy was characterized by premature labor, breech presentation, and poor progression of labor. Cesarean section under general anesthesia had been performed with no record of complications except the need for a postpartum blood transfusion. At birth her first child was found to have club feet and clinical signs and symptoms resulting in the diagnosis of myotonic dystrophy for both mother and child at that time. Family history confirmed the diagnosis (Fig. 1). In contrast, the second pregnancy was complicated by severe exacerbations of myotonia and weakness. On admission, she was in labor with a poor quality of uterine contractions.

Physical examination revealed a woman with a flat, sad-looking face due to facial arthralgia (Fig. 2) and weak and atrophic masseter, temporalis, and distal limb muscles (Fig. 3). She also exhibited dysarthria, delayed decontracture of her grip, and percussion myotonia of thenar and forearm muscles. Electrocardiography showed a first degree heart block, but no other abnormalities of rate or rhythm.

The patient was brought to the operating room in active labor with cervical dilation of 3 cm. No preoperative medication was given. After intravenous volume loading with 800 ml Ringer's lactate solution, spinal anesthesia was induced with 14 mg tetracaine in divided doses (8 + 6 mg) injected in the L3–4 interspace, with resulting anesthesia to T5 bilaterally. Twenty min later a viable female infant was delivered with Apgar scores of 5 at 1 min and 8 at 5 min. Oxytocin infusion (30 units/L) was begun immediately. A densely adherent placenta was found in the anterior lower uterine segment, requiring manual extraction. During placental extraction severe uterine contractions began, followed by waves of relaxation accompanied by hypotension (systolic blood pressure 75

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Address correspondence to Dr. Cope, Department of Anesthesiology, University of South Alabama Medical Center, 2451 Fillingim Street, Mobile, AL 36617.

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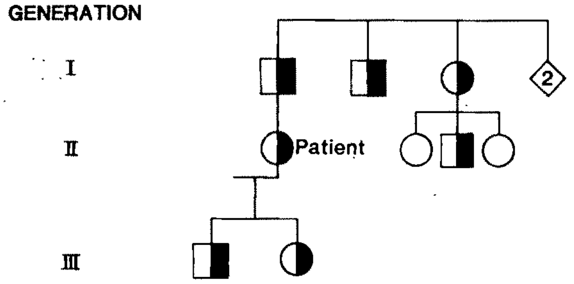

Figure 1. Affected members of the parturient's family show the strong genetic predisposition to myotonic dystrophy. However, diagnosis was not established in our patient until after the birth of her first child. Symbols: ◨, male carrier; ◑, female carrier; ○, unaffectd female; ◇, 2 siblings of undetermined sex.

torr), which responded to a small dose of ephedrine (10 mg intravenously).

Spinal anesthesia to T5 bilaterally was effective for incision and delivery. However, during and after placental extraction, the patient complained of severe pain coincident with alternating uterine contractions and relaxation accompanied by a brisk increase in bleeding: (375 ml over 2–3 min). These uncoordinated cycles of uterine spasm/atony failed to respond to uterine massage or oxytoxics.

We suggested that direct application of local anesthetic to cut muscle bundles might influence local uterine muscular activity, and on this basis the surgeons topically applied 30 ml of 0.5% bupivacaine over the cut surface of the myometrum where contractions were most severe.

Uterine contractions decreased in severity almost immediately, and at 5 min all cycles of aberrant spasms followed by atony ceased. Bleeding stopped, and the surgeons proceeded to complete the uterine repair and bilateral tubal ligation without further complications. The patient continued to be hemodynamically stable with no episodes of hypotension or myocardial conduction defects. Neither were there central nervous system symptoms suggestive of toxicity from the 150 mg of topical bupivacaine.

Approximately 2 hr after delivery, there was a decrease in systolic blood pressure to 80 torr, with a pulse of 94, again accompanied by uncoordinated waves of uterine relaxation and spasm (dystonia). A 300-ml vaginal loss of blood was noted. These symptoms abated with manual uterine massage, methergine (0.2 mg. intravenously), and prostaglandins (Prostin 15 M, 0.25 mg intramuscularly), but a decrease in hematocrit ensued from 32.3% preoperatively to 21.6%. Transfusion of four units of packed red blood cells restored the hematocrit, and the patient remained hemodynamically stable postoperatively.

Discussion

The obstetrical complications of myotonic muscular dystrophy commonly reported and seen in our patient include premature onset of labor, abnormal progression of labor, uterine atony, and postpartum hemorrhage. In addition, unlike this patient's first pregnancy, uterine muscle contractures during this gestation were severe enough to cause her to visit the emergency room several times. She also experienced severe intermittent weakness, which made any household work impossible. Prior to her first pregnancy she had experienced only mild episodes of weakness and myotonia and during that pregnancy had only minimal exacerbation of her symptoms. Past reports confirm the deleterious effect of pregnancy on the symptoms of myotonic dystrophy (4,6).

General anesthesia in patients with myotonic dystrophy is often associated with severe cardiovascular and respiratory complications; exaggerated responses to barbiturates, narcotics, halothane, and diazepam; myotonic contractions after depolarizing muscle relaxants; inability to handle secretions; prolonged postoperative tracheal intubation; and bradycardia that is unresponsive to atropine (8–12). There are reported cases of severe laryngeal spasm on induction with death ensuing. Regional anesthesia has been recommended, but incomplete motor block and shivering sufficient to stimulate myotonic contractures have been reported with epidural anesthesia (13,14). In the one report of spinal anesthesia for cesarean section, severe postpartum hemorrhage necessitated an emergency hysterectomy after refractory uterine atony (8).

In these patients, dystonia results from abnormal calcium metabolism at the cellular level in which the Ca^{2+} ATPase system fails to return to Ca^{2+} to the sarcoplasmic reticulum. Unsequestered Ca^{2+} then remains available for activating contraction, and results in continued spasm and counterspasm in the muscle tissue (7,8,15). Therefore, neither general anesthesia, anesthesia at the spinal nerve level, nor paralysis of neuromuscular transmission will suppress this abnormal muscle activity. However, direct application of local anesthetic to the muscle membrane may be expected to produce a more stable membrane. Indeed, Wheeler and James (16) reported local applications of 0.5% bupivacaine for a laparoscopic tubal ligation without systemic or muscle complications.

In our case we combined spinal anesthesia with the topical application of bupivacaine to the uterus to achieve block at both the spinal nerve level and the muscle itself. We are uncertain whether the uterine atony that developed in the recovery room was secondary to the wearing off of bupivacaine or was an

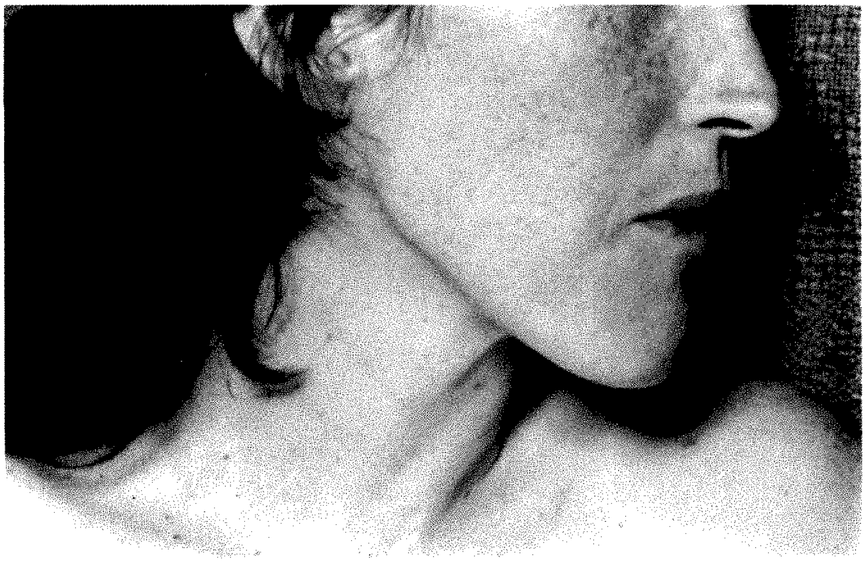

Figure 2. The patient's face is characteristic of myotonic dystrophy with atrophic facial musculature, resulting in gaunt facies and ptosis. Sternocleidomastoid and shoulder musculature also are affected.

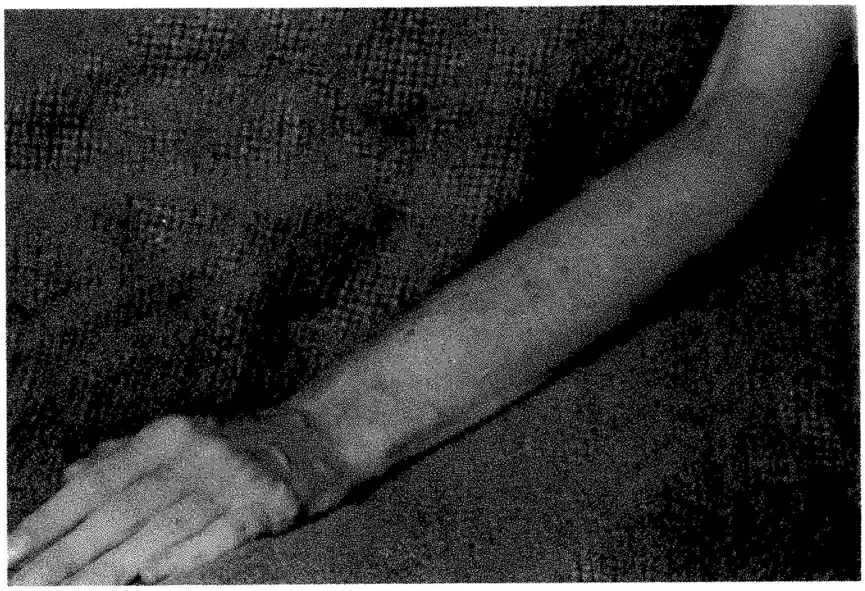

Figure 3. Distal atrophy of left forearm and hand musculature.

inevitable result of irregular calcium metabolism in the uterine muscle. Nevertheless, the combination of spinal with topical local anesthesia applied directly to the uterus may be a valid alternative approach to avoid a major problem associated with anesthesia in the myotonic parturient.

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Chloral Hydrate:

A Potential Cause of Arrhythmias

Irving A. Hirsch, MD, and Howard L. Zauder, MD, PhD

Chloral hydrate and its derivatives are considered to be relatively nontoxic hypnotic drugs recommended for sedation of pediatric and geriatric patients. In therapeutic doses, blood pressure and respiration are only minimally affected. However, there have been reports of cardiac dysrhythmias after chloral hydrate poisoning and toxic doses produce severe respiratory depression and hypotension. We now report four cases of supraventricular tachycardia (SVT) occurring after administration of chloral hydrate to children who were receiving vasoactive drugs after surgical correction of complex congenital heart disease.

Case 1

A 9-yr-old, 25-kg girl with complicated congenital heart disease presented for surgical amelioration of severe hypoxemia. Postoperatively, she was admitted to the pediatric intensive care unit and required mechanical ventilatory support and continued infusion of isoproterenol, 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and dopamine, 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$, for circulatory support. The sinus rhythm present preoperatively persisted into the immediate postoperative period. Chloral hydrate, 600 mg, every 6 hr (96 $mg \cdot kg^{-1} \cdot day^{-1}$) was administered for sedation. Seven hours postoperatively, the patient developed supraventricular tachycardia (SVT) with a rate of 220 beats/min. This was successfully treated with verapamil, 0.1 mg/kg, and divided doses of digoxin (total 1 mg). The SVT recurred within 4 hr and responded only to propranolol. Despite normal laboratory studies, episodes of SVT persisted. The isoproterenol infusion was reduced to 0.008 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and dopamine continued at 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ without improvement. After discontinuation of chloral hydrate and continued administration of propranolol, SVT did not recur. Eventually the β-antagonist was discontinued, but although dopamine and isoproterenol were continued at the previous rates, there was no return of SVT. She was slowly weaned from inotropic support and was discharged from the hospital.

Case 2

A 30-month-old, 14.4-kg girl with Down's syndrome and a Type C complete atrioventricular canal defect accompanied by pulmonary hypertension had surgical repair of the AV septal defect and AV commissurotomy. Postoperatively, isoproterenol, 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and dopamine, 5 $\mu g \cdot kg^{11} \cdot min^{-1}$, were required for cardiovascular support. The patient was agitated and received two doses of chloral hydrate, each 700 mg, per rectum. She subsequently developed SVT. The dose of chloral hydrate was changed to 350 mg every 4 hr (146 $mg \cdot kg^{-1} \cdot day^{-1}$). On the third postoperative day, while receiving isoproterenol, 0.12 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and dopamine, 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, she again developed SVT, which was treated with digoxin and propranolol. Dysrhythmias persisted for 3 days until chloral hydrate was discontinued. Inotropic agents were continued without recurrence of SVT. She was slowly weaned from inotropic support and had an otherwise uneventful hospital course.

Case 3

A cyanotic, 10-month-old male infant underwent complex intracardiac surgery. He had a stormy postoperative course and required prolonged ventilatory support. Increasing doses of chloral hydrate (up to 500 $mg \cdot kg^{-1} \cdot day^{-1}$) were used for sedation. On the second postoperative day, SVT, initially responsive to digoxin, developed. On the ninth postoperative day, persistent SVT developed, which was responsive only to propranolol. Arrhythmias continued for 4 days. On the fourteenth postoperative day, chloral hydrate was discontinued and dysrhythmias did not recur. The patient had a prolonged hospital stay due to continued respiratory failure.

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Address correspondence to Dr. Hirsch, Department of Anesthesiology, 750 E. Adams St., Syracuse, NY 13210.

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Case 4

A 5-month-old, 5.3 kg male infant with complex congenital heart disease and chronic congestive heart failure underwent repair of ventricular and atrial septal defects. Postoperatively, chloral hydrate, 250 mg, every 3–4 hr (283 $mg·kg^{-1}·day^{-1}$) was administered for sedation. On the third postoperative day he developed SVT, which was treated with digoxin. Dysrhythmias ranging from SVT to bradycardia recurred through postoperative day 5, at which time he suffered cardiac arrest and was successfully resuscitated. Chloral hydrate was discontinued on the eighth postoperative day, but bradycardia persisted and cardiac pacing was required. The patient had a very difficult hospital course but SVT did not recur.

Discussion

Toxic effects of chloral hydrate include central nervous system depression, hypotension, gastric irritation, hepatic damage, and albuminuria. Depression of myocardial contractility and shortening of the refractory period have also been noted (1). Chloral hydrate intoxication has been reported to cause cardiac arrhythmias (2–7). In all reported cases, ventricular and supraventricular arrhythmias severe enough to require treatment developed after administration of large doses of chloral hydrate.

Marshall (4) suggested that chloral hydrate and its breakdown product trichloroethanol may sensitize the myocardium to circulating catecholamines. Large doses of catecholamines have been previously shown to cause cardiac arrhythmias in unanesthetized patients; in the presence of halogenated hydrocarbons there is a marked decrease in the dose of catecholamine required to produce these arrhythmias (8). The β-adrenergic blocking agents consistently and specifically abolish both these arrhythmias and those due to intoxication with the halogenated hydrocarbons such as chloral hydrate and trichlorethanol (2,4,5,7). Other proposed mechanisms for chloral hydrate-induced arrhythmias include enhanced automaticity of supraventricular and ventricular pacemaker cells (7). Shortening of the myocardial refractory period observed after large doses may be of importance as well (7).

Most of the published case reports of the chloral hydrate overdose occurred in subjects without evidence of underlying heart disease. However, patients with heart disease may also show untoward cardiac effects with toxic doses of chloral hydrate (1). Case numbers 3 and 4 seem to be examples of chloral hydrate intoxication with doses of 500 and 283 $mg·kg^{-1}·day^{-1}$, respectively. Case numbers 1 and 2 did not receive toxic doses (96 $mg·kg^{-1}·day^{-1}$ and 146 $mg·kg^{-1}·day^{-1}$, but were receiving inotropic support. The four patients we describe were a high-risk group in whom the incidence of postoperative arrhythmias is considerable regardless of drug intervention. The direct relationship of chloral hydrate and arrhythmias thus remains unproven in these complicated cases. Nevertheless, the possibility for pharmacologic interaction remains, especially if chloral hydrate has the potential to act as a sensitizing agent.

In summary, chloral hydrate is usually a safe hypnotic drug for sedation with minimal respiratory and cardiovascular effects. However, we encountered four complicated cases of supraventricular tachycardia after administration of chloral hydrate in children after surgery for congenital heart disease. Two cases were presumably due to unintentional overdosage, whereas two cases may represent sensitization of the myocardium. These cases emphasize the arrhythmogenic potential of chloral hydrate.

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Delivery Temperature of Heated and Cooled Intravenous Solutions

Edward A. Norman, MD, Idrees Ahmad, MD, and Norman J. Zeig, MD

Maintaining normothermia is an important duty of the anesthesiologist. The goal of this study was to determine the maximum temperature to which an intravenous container may be heated and still deliver its contents to the patient at or slightly below body temperature. Our department stores containers of lactated Ringer's solution in the warming cabinets in the operating room (OR) prior to use. We measured temperatures in and on the container and along the intravenous tubing. A trial of cold normal saline from the OR refrigerator was also used to evaluate heat gain during an infusion such as would be used during treatment of malignant hyperthermia.

Methods

New 1000-ml containers of lactated Ringer's solution in Lifecare Flexible Intravenous Containers (Abbott Laboratories, North Chicago, IL) were placed in operating room warming cabinets at 44, 50, 55, and 60°C. A skin temperature probe was placed at the base of each bag, and a tympanic temperature probe with the plastic sheath removed was placed through the injection port into the center of the lower portion of the bag (Fig. 1). The probes were attached to the Mon-A-Therm temperature probe terminal, model 6000, with a three-channel adapter (Mon-A-Therm, Inc., St. Louis, MO). When the two bag temperatures were equal, the intravenous solution container was removed from the warming cabinets. Room temperatures during all trials ranged from 23 to 25°C.

The intravenous fluid containers were hung 208 cm from the floor. Abbott Laboratories non-vented 195-cm intravenous tubing and 80-cm extension tubing were connected to the container. Temperature was also measured at the point of connection of the two pieces of tubing, and at the terminal end of the extension tubing (Fig. 1). Care was taken to ensure that no surface of the intravenous bag or intravenous tubing touched any surface unless insulated. The terminal end of the tubing was 90 cm from the floor.

When all connections were made and the system had been calibrated and inspected for errors, internal and external bag temperatures were measured. Flow rate was preset at 1000 or 500 ml/hr. Temperature measurements were made at all four sites at 1 min and 5 min, and thereafter at 5-min intervals for 60 min. Temperature was then measured every 15 min for the next 60 min. Room temperature was determined during each trial with a rectal temperature probe allowed to hang freely in the room. Five trials were made at each temperature and rate. The mean was used for calculations.

On a separate day, 1000-ml containers of normal saline were removed from the anesthesia work room refrigerator where the temperature is maintained at 4°C. Trials were conducted in the same way as those in which warmed fluids were used.

In an additional trial, 1000-ml containers of lactated Ringer's solution were wrapped with "egg-crate" foam rubber comfort pads (Bio-Clinic Company, Rancho Cucomonga, CA). Initial internal container temperature was 50°C, and the rate was set at 1000 ml/hr.

For control, intravenous containers at room temperature were used. Studies were again conducted as with the above warmed solutions.

Results

Intravenous containers of lactated Ringer's solution, which left the operating room warmers at 50.0°C and were set to deliver fluid at a rate of 1000 ml/hr, had mean temperatures of 49.6 ± 0.50°C (SD) in the center of the container (T1) and 43.5 ± 1.42°C on the surface of the container (T2) at time zero. After 1 min, temperatures averaged 48.5 ± 0.55°C and 43.4 ± 0.83°C,

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Address correspondence to Dr. Norman, Dept. of Anesthesia, Humana Hospital Sun Bay, 3030 6th Street South, St. Petersburg, FL 33705.

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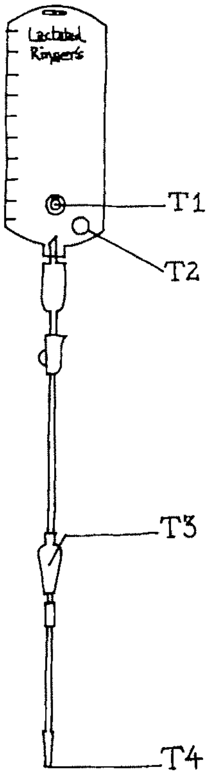

Figure 1. Locations of temperature measurements. T1 is inside the IV container. T2 is on the surface of the IV container. T3 is at the connection of the nonvented IV tubing and proximal end of the extension tubing. T4 is at the distal end of the IV extension tubing.

respectively. The temperature at the junction of nonvented intravenous tubing and extension tubing (T3) averaged 39.6 ± 0.72°C, and at the distal end of the extension tubing (T4) 37.0 ± 1.07°C. During the next 5 min, tubing temperatures increased slightly to 39.7 ± 0.51°C and 37.2 ± 0.63°C. Internal and external bag temperatures declined. At 1 hr, T3 was 32.6 ± 0.76°C, and T4 was 31.0 ± 0.68°C (Fig. 2). Containers with an initial temperature of 44.0°C that delivered fluid at a rate of 1000 ml/hr were associated with mean temperatures at T4 of 32.6 ± 0.62°C, 33.9 ± 0.81°C, and 28.0 ± 0.99°C at 1 min, 5 min, and 1 hr, respectively.

At 60.0°C and an intravenous rate of 500 ml/hr, T1 and T2 were 58.8 ± 0.25°C and 53.5 ± 1.21°C, respectively. At 1 min, container temperature decreased to 57.7 ± 0.35°C and 52.6 ± 0.98°C. The temperature at T3 was 30.2 ± 1.56°C and 25.0 ± 1.82°C at T4. At 5 min, T3 was 38.9 ± 0.62°C and T4 was 36.0 ± 0.51°C. At 1 hr, T3 and T4 were 33.1 ± 0.91°C and 30.1 ± 0.87°C, and at 2 hr 27.5 ± 1.43°C and 27.0 ± 1.37°C, respectively (Fig. 3). At 55.0°C, T3 was 30.4 ± 0.75°C at 1 hr and 26.2 ± 0.83°C at 2 hr, and T4 was 28.9 ± 1.51°C and 25.6 ± 1.61°C at 1 hr and 2 hr, respectively.

Normal saline, which left the refrigerator at 4.0°C and ran at a rate of 1000 ml/hr, had T1 and T2 values of 4.6 ± 0.75°C and 5.2 ± 1.05°C at time zero. At the end of 1 min, T3 was 14.5 ± 1.10°C and T4 was 18.0 ± 1.30°C. The tube cooled over the next 5 min, and these two temperatures decreased to 11.9 ± 0.71°C and 13.7 ± 0.84°C respectively. At 1 hr, T1 was 13.5 ± 1.26°C and T2 was 14.2 ± 1.08°C, with T3 reading 16.4 ± 1.32°C and T4 reading 17.3 ± 1.28°C (Fig. 4). If the intravenous rate was decreased to 500 ml/hr, delivery temperatures were 15.8 ± 0.77°C, 15.7 ± 1.01°C, 17.7 ± 1.21°C, and 20.8 ± 1.54°C at T3 at 1 min, 5 min, 1 hr, and 2 hr, respectively.

The insulated trial started with a T1 of 50.0°C. The distal extension tubing at 5 min gave a temperature reading of 37.0 ± 0.77°C, almost equal to the trial with no wrap, 37.2 ± 0.63°C. However, at 1 hr, temperature at the same location decreased only to 33.8 ± 0.88°C, 3°C higher than the unwrapped trial.

The control trial began with T1 and T2 temperatures of 22.9 ± 0.41°C and 23.0 ± 0.39°C, respectively. At one hr, a temperature of 23.6 ± 0.50°C at both T3 and T4 was recorded (Fig. 5). Room temperature during the same hour was manually set to increase from 23.5 ± 0.37°C to 24.5 ± 0.33°C.

Discussion

The effect of anesthesia on thermoregulation has been well-studied. Shivering increases oxygen demand by as much as four hundred–five hundred % (1). This is especially significant in infants who have unreliable shivering mechanisms (2) and in elderly or sick patients who have difficulty increasing their O_2 supply (3,4,5). Body heat production is about 2500 kcal/day or 100 kcal/hr. Each 1000 ml of fluid administered that differs by 1°C from 37°C poses a burden of 1000 calories or 1 kcal. If 1000 ml of intravenous fluid is administered at a room temperature of 22°C, the body must expend 15 kcal to compensate for the cool fluids. This is 15/2500 or about 0.6% of the daily heat production or 15% of heat production/hr. Warming of intravenously administered fluids, especially blood, prevents unintentional hypothermia (6).

In our study, we attempted to find an inexpensive and readily available method for administering warm intravenous solutions. Although fluid warmers are the ideal way to warm intravenous fluids, they are expensive. It is often not practical to have one fluid warmer for every operating room. Every operating suite is equipped with warmers in which blankets, irrigation solutions, and intravenous fluids can be warmed.

At 1000 ml/hr, initial internal container tempera-

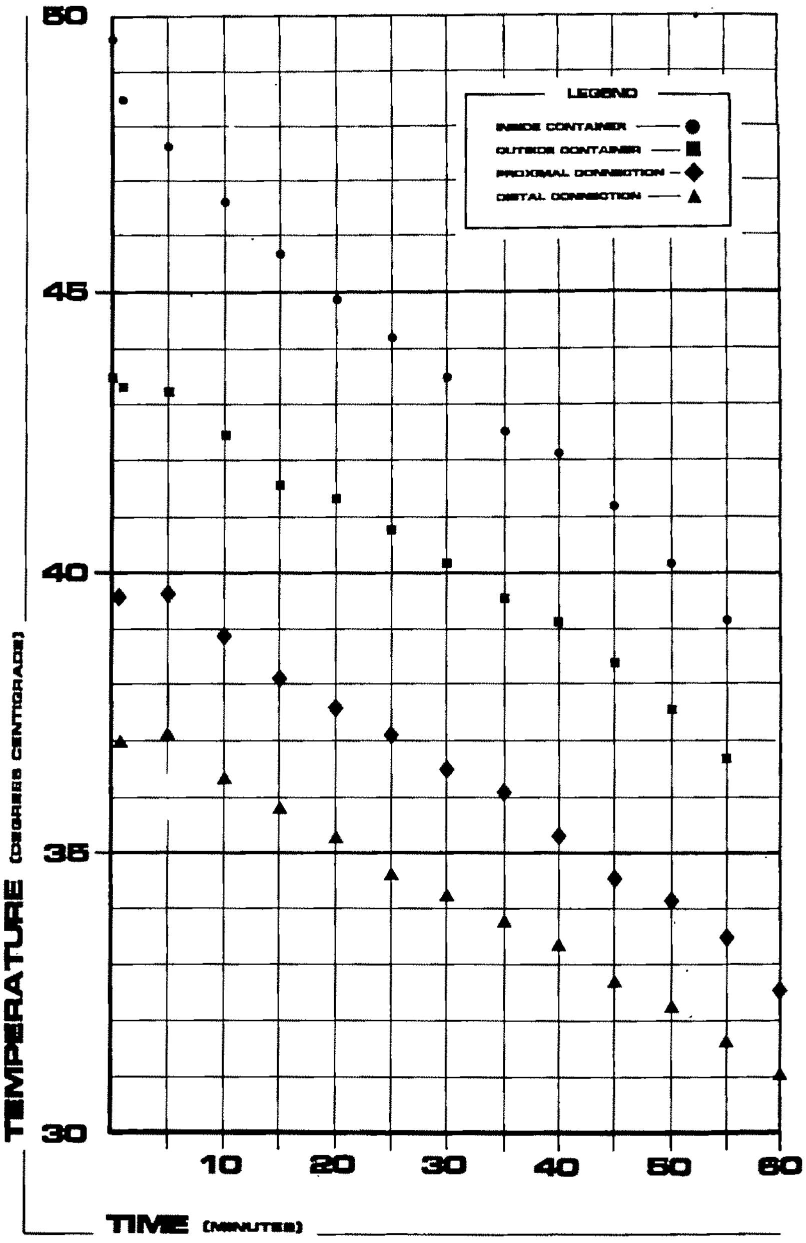

Figure 2. One liter of lactated Ringer's solution heated to 50°C and run at a rate of 1000 ml/hr, recorded at 1 min, then at 5-min intervals over 1 hr. Data points are means (n = 5).

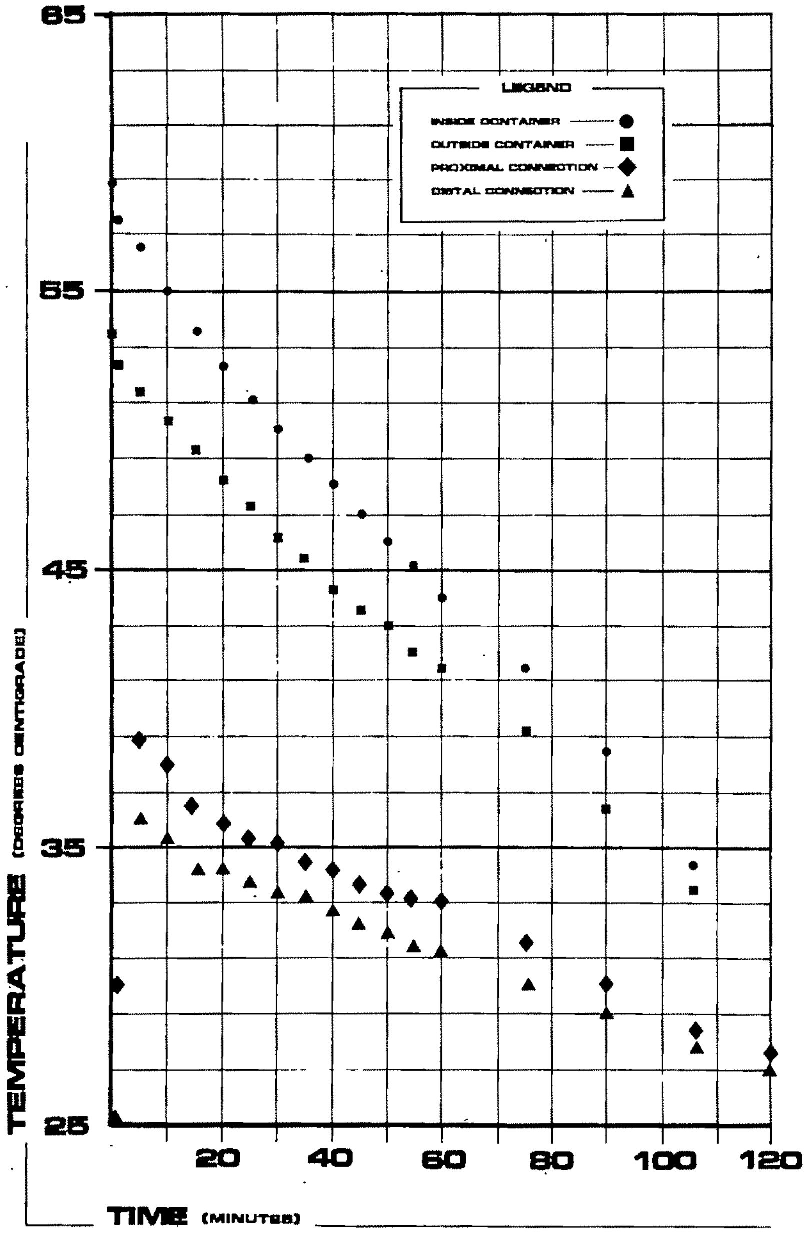

Figure 3. One liter of lactated Ringer's solution heated to 60°C and run at a rate of 500 ml/hr, recorded at 1 min, then at 5-min intervals over 1 h, then at 15-min intervals during the second hr. Data points are means ($n = 5$).

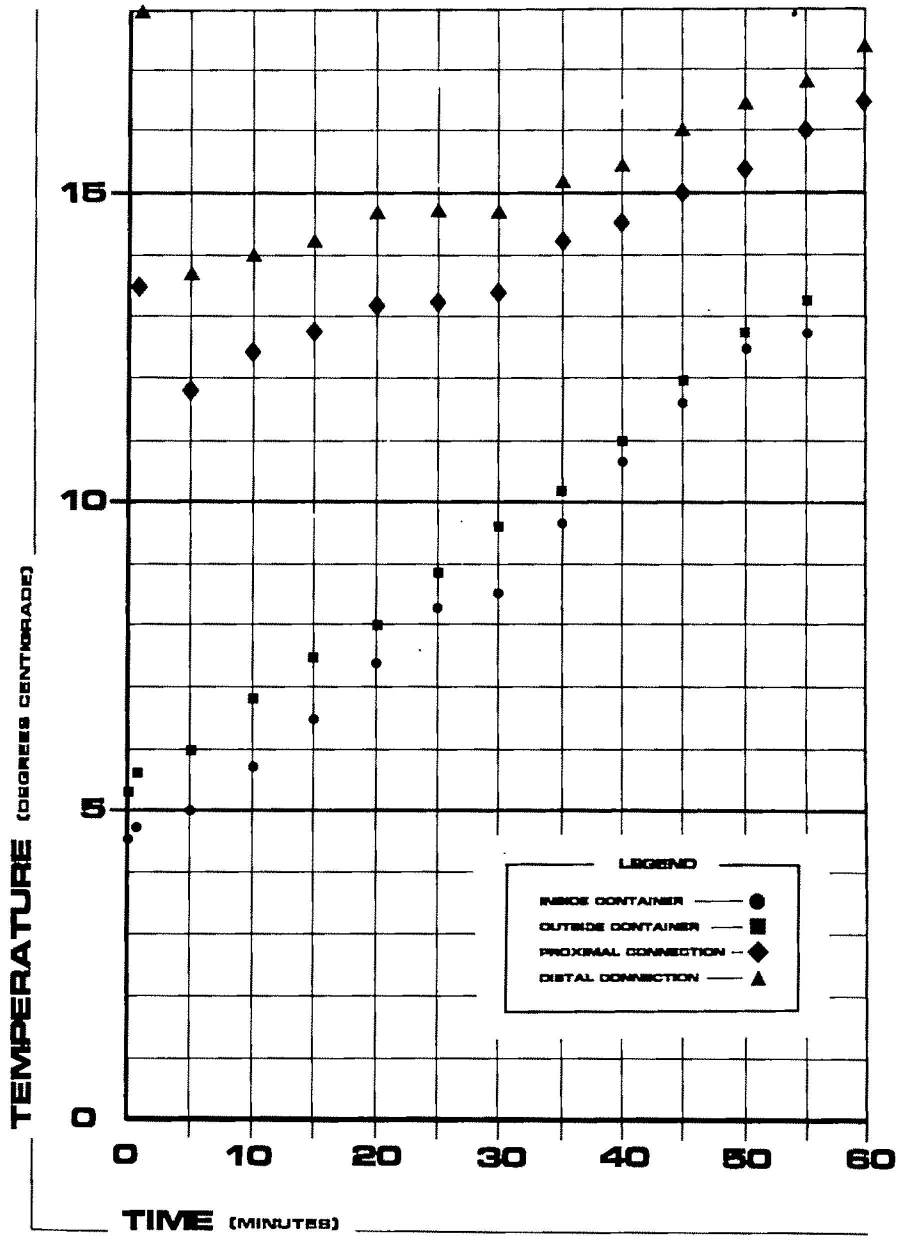

Figure 4. One liter of normal saline solution cooled to 4°C and run at a rate of 1000 ml/hr, recorded at 1 min, then at 5-min intervals over one hr. Data points are means ($n = 5$).

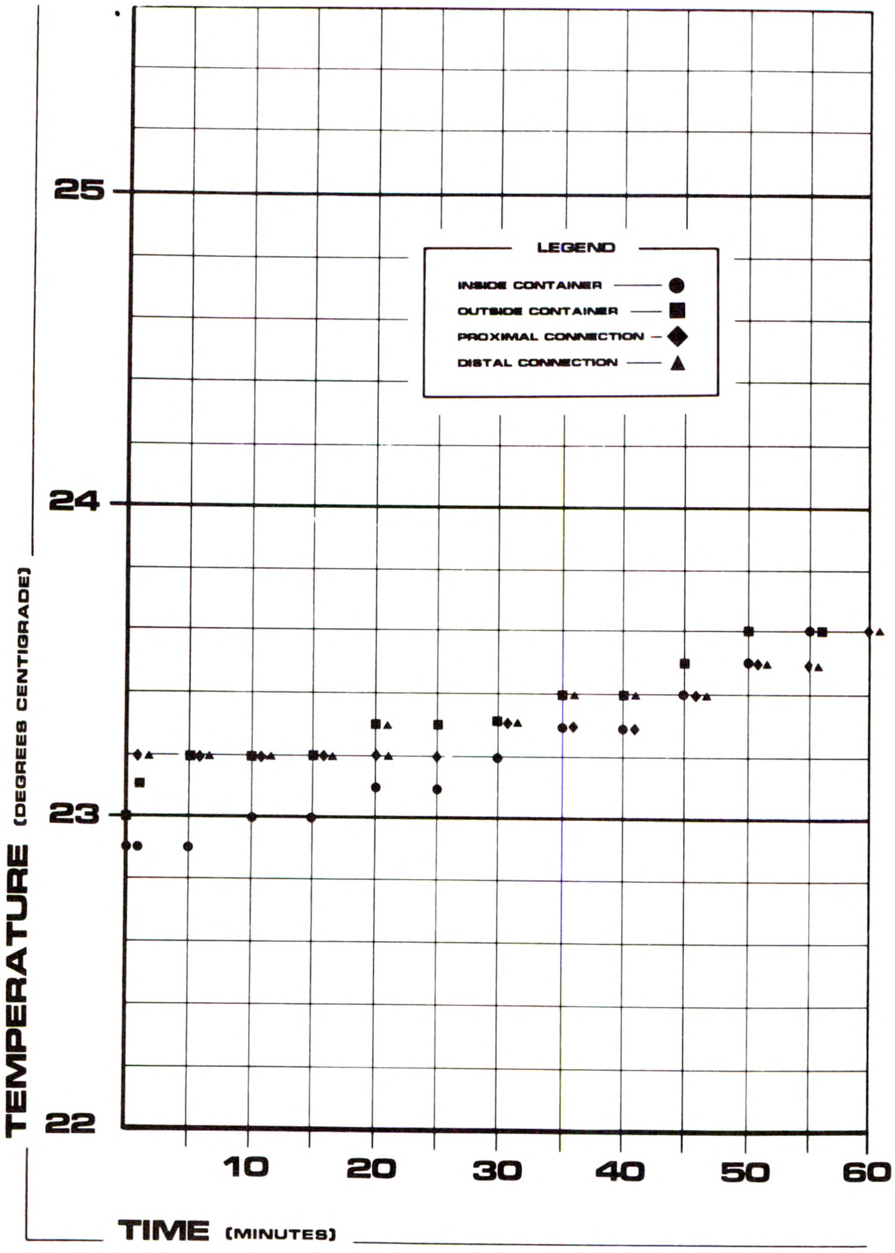

Figure 5. One liter of lactated Ringer's solution at room temperature run at a rate of 1000 ml/hr as a control, recorded at 1 min, then at 5-min intervals over 1 hr. Data points are means (n = 5).

ture may be 50°C, and at 500 ml/hr the container may be warmed to 60°C. Abbott Laboratories suggests that the container not be warmed above 65°C. Therefore we recommend that 60°C be the maximum warmer temperature. No dextrose-containing solution should be heated because the dextrose will be altered by heat.

When warm intravenous fluid is used, delivery temperature increases during the first 5 min secondary to heating of the intravenous tubing. Thereafter, a linear decline in temperature occurs. A higher delivery temperature could be achieved if the intravenous extension tubing were removed (Figs. 2,3). However, it is more practical to change the intravenous container to a new warm container every hr if the rate is less than 1000 ml/hr. If a second length of extension tubing is added, the delivery temperature can be decreased. Normal saline cooled to 4°C used to treat malignant hyperthermia quickly gains heat (Fig. 4). After other lifesaving measures have been instituted, it would be advantageous to the patient to remove the intravenous extension tubing. Our control showed that the intravenous container and intravenous tubing are sensitive to small changes in room temperature (Fig. 5). Further reduction of heat loss or heat gain from the intravenous tubing or intravenous container may be accomplished by insulating the bag. Because the container temperature does not increase, there is no danger of exceeding the 37°C delivery temperature at the distal extension tubing.

Care was taken to measure both external and internal container temperatures because the anesthesiologist will assess an intravenous container by its external temperature once it has been removed from a controlled environment such as a warmer or refrigerator. Internal and external temperatures varied by 2–6°C depending on the time of measurement. The greatest difference was at time zero. In general, intravenous containers at temperatures of 50–60°C are hot to the touch and difficult to handle.

In conclusion, the authors have quantified an inexpensive and easy method to help maintain normothermia. It is certainly not the only method that could be employed. Heating and cooling of intravenous fluid becomes less effective as the container temperature approaches room temperature. In addition, the delivery temperature of the warmed fluid is below body temperature for the majority of its administration. Warming the fluid does not truly warm the patient, but it greatly reduces the cooling effect of fluids administered at room temperature. In the case of malignant hyperthermia, the shortest tubing from bag to vein should be used, and if the intravenous rate must be below 1000 ml/hr then the container should be changed after each hour and replaced with a new cool container from the refrigerator.

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Does Topical Anesthesia of the Sphenopalatine Ganglion with Cocaine or Lidocaine Relieve Low Back Pain?

Jerry J. Berger, MD, Stephen T. Pyles, MD, and Segundina A. Saga-Rumley, MD

Sphenopalatine ganglion block has been advocated in the past for relieving muscle spasm, neuralgia, vasospasm, reflex sympathetic dystrophy, low back pain, low back strain, sciatica, and angina (1,2), although no well-controlled studies have been published. Classically, cocaine has been used for this block. The present study was undertaken to determine the duration of action and efficacy of sphenopalatine ganglion block for relief of chronic low back pain and to compare the efficacy of cocaine with that of lidocaine and a placebo.

Materials and Methods

Twenty-one consecutive patients (nine men and 12 women aged 21–70 yr) treated at our pain clinic for chronic low back pain, i.e., low back pain unrelieved by most acceptable surgical and nonsurgical methods, participated in this double blind study, which was approved by the committee on human experimentation. Either normal saline, 10% cocaine, or 4% lidocaine (Xylocaine) was applied topically to the sphenopalatine ganglion by placing a pledget soaked with one of the solutions on an applicator and passing it bilaterally along the inferior and middle turbinates of the nose until contact with the sphenoid bone. The pledget was left in place for 30 min.

Each patient was treated in the morning and in the afternoon on two consecutive days. The degree of pain was graded by asking the patient to judge it on a scale of 0 (no pain) to 10 (the worst pain the patient had experienced), and effect of treatment on pain was noted simply as a change in pain score, e.g., from 10 to 5. Pain score was evaluated before the first treatment; 1 hr after the second treatment on the first day; 1 hr after the fourth treatment on the second day (the last treatment); and 1 day, 1 week, and 1 month after the last treatment.

Data for each time period were analyzed by the Kruskal–Wallis test for statistically significant differences between median pain scores and, for each drug, by the Wilcoxon signed rank test for any difference in pain before the nerve block compared with any time after it (the actual permutation distribution of the statistic was generated). Analysis of baseline pain scores showed that pain before treatment did not differ among treatment groups ($P < 0.05$); thus comparison of the groups was valid.

Results

The difference in effectiveness of the three treatments in relieving low back pain was statistically significant 1 week after the last treatment (Table 1). At 1 week, the saline treatment group had a significantly higher median pain score than the group with lidocaine. The effect of cocaine on back pain was not quite statistically significant ($P = 0.0594$). No patient had statistically significant pain relief with saline. At 1 month, there was no statistical difference among the treatment groups in the degree or frequency of pain relief. At this time, only four out of the 15 patients anesthetized with either local anesthetic rated pain more than one point lower than baseline; of the seven control patients, only one rated back pain more than one point lower. No other differences were found between the treatments at the other time periods.

Data from before the block were compared with those afterward to determine at what time the treatment started to take effect. No statistical differences were found at the 0.05 level; therefore, the exact time during the study when pain relief began could not be determined.

Discussion

The sphenopalatine ganglion, located in the pterygopalatine fossa posterior to the middle turbinate, is

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Address correspondence to Dr. Berger, Department of Anesthesiology, Box J-254, J. Hillis Miller Health Center, Gainesville, FL 32610-0254.

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Table 1. Low Back Pain Scored on a Scale of 0 (No Pain) to 10 (Worst Pain Experienced) after Sphenopalatine Ganglion Block with 10% Cocaine, 4% Lidocaine, or Saline

Drug	Pain score					
	Before treatment	During treatment		After treatment		
		1 hr	*48 hr*	*1 day*	*1 week*	*1 month*
Cocaine (*n* = 7)	2	2	7	7	2	2
	5	2	2	1	1	6
	5	3	0	0	1	4
	5	5	1	3	5	5
	5	5	4	5	5	4
	7	0	3	2	2	4
	10	10	10	10	10	10
Lidocaine (*n* = 7)	4	6	5	5	5	5
	7	7	7	4	1	2
	7	9	4	8	8	ND[a]
	8	4	6	1	6	7
	8	8	10	10	5	5
	10	0	1	0	1	10
	10	5	3	3	2	2
Saline (*n* = 7)	5	5	2	7	8	8
	6	6	3	3	6	6
	7	7	7	7	7	10
	8	7	0	3	5	5
	8	8	8	8	8	8
	9	9	3	10	10	10
	9	9	10	10	10	10

[a] Not determined because patient received an epidural steroid injection.

covered by only a 1- to 5-mm layer of connective tissue and mucous membrane. Topically applied local anesthetics can, therefore, diffuse into the ganglion. The sphenopalatine ganglion has major branches to the trigeminal nerve, the facial nerve, and the carotid plexus, the latter communicating directly with the superior cervical sympathetic ganglion. The sphenopalatine ganglion has sensory, visceral motor (parasympathetic), and sympathetic functions.

Parasympathetic activity of the sphenopalatine ganglion is mediated via the superficial petrosal nerve; the branches going to the lacrimal gland may explain the excessive lacrimation associated with stimulation of the sphenopalatine ganglion. The sympathetic root is the great deep petrosal nerve, an extension of the cervical sympathetic chain. Fibers from cell bodies in the ventral horn of the thoracolumbar spinal cord communicate directly or via cervical ganglion synapses with the sphenopalatine ganglion (1).

Block of the sphenopalatine ganglion to relieve intractable pain received little attention until the nasal application of cocaine over the sphenopalatine ganglion was reported to control painful vascular and muscular spasms (3). Kuntz was asked in 1935 to explain how anesthetizing the sphenopalatine ganglion could relieve lumbar pain and he replied, "Pain seems to have been relieved in the lumbar region, but I am sure we have no explanation at the present" (4).

In an ongoing clinical study of acute back pain in patients aged 18–65 yr, Reder et al. applied either 10% cocaine or a placebo to the sphenopalatine ganglion to evaluate possible pain relief (1). Among patients given cocaine, 25% had no pain relief and 73% improved; 45% of the latter had marked to complete improvement after a single application. In the control group, 25% were improved and 75% were not.

Our study compared the effects of topical saline, 10% cocaine, and 4% lidocaine for anesthetizing the sphenopalatine ganglion to treat chronic low back pain. Because of the subjective nature of low back pain, evaluation of pain relief is difficult. Nevertheless, in our study, sphenopalatine ganglion block was judged by seven out of 15 patients who received either cocaine or lidocaine to have decreased the intensity of their low back pain for one week as reflected by a decrease in pain score (e.g., from 8 to 5). Saline at 1 week only decreased the pain score in one out of seven patients, less than the percentage normally relieved with a placebo. This low percentage might be explained by the fact that, with saline, subjects did not experience numbness of the nasopharyngeal mucosa and thus might have realized they received the placebo.

Though clinical pain relief started after the last block, pain relief was not statistically significant until 1 week after the last treatment. The exact time when pain relief peaked could not be determined because pain scores were not evaluated between the second and sixth day after treatment.

Four percent lidocaine was effective in decreasing the intensity of low back pain; 10% cocaine was almost as effective. In a study that compared intranasal cocaine and lidocaine, experienced drug abusers were unable to discriminate between these two drugs (5). Plasma levels of lidocaine were similar to those of cocaine after intranasal application of the same dose. Our finding of almost similar pain relief with either drug would not be unexpected in light of the previous study (5).

That low back pain is relieved by sphenopalatine ganglion block cannot be readily explained on physiologic or anatomic grounds, even though such relief has been claimed periodically since 1925 (3,6). In lower animals the sphenopalatine ganglion probably has a role in the rage reaction. It is a major point of entry of the autonomic system, which can be modulated by anesthetizing the ganglion. Procacci et al. (7) reported changes in cutaneous pain threshold after sympathetic block in reflex dystrophy, which indicates that there is abnormal sympathetic reflex activity in many differently classified diseases, along with myalgic spots (trigger points) in patients suffering from reflex sympathetic dystrophy. With block of the sympathetic chain, Procacci et al. noted a lessening of trigger point pain. Some have thought that sphenopalatine ganglion block relieves pain psychosomatically, but Ruskin (8) stated that psychosomatic symptoms probably are mediated by the autonomic system and, therefore, the block most probably has a physiologic basis, as suggested by Procacci et al.

Although the time at which the anesthetic took effect was difficult to pinpoint, this study showed a decrease in intensity of low back pain between the time of the last block of the sphenopalatine ganglion and 1 week afterward. However, long-lasting relief (1 month duration) was not evident; therefore, clinical use of sphenopalatine blocks in patients with chronic low back pain would be of only limited value. If relief is truly mediated by the autonomic nervous system, then study with sympatholytic agents may be warranted. Why maximal relief was not immediate requires further investigation with more frequent evaluation of pain between the first and seventh day after the block.

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High-Dose Sufentanil:

Four Cases of Sudden Hypotension on Induction

Bruce D. Spiess, MD, Rodney H. Sathoff, MD, Abdel R. S. El-Ganzouri, MD, and Anthony D. Ivankovich, MD

Sufentanil, an N_4-substituted derivative of the synthetic narcotic fentanyl, has recently been released for clinical usage. High-dose opiate anesthesia has been a well-accepted technique for cardiac surgery since Lowenstein et al. (1) published their work using morphine, 1–3 mg/kg. Fentanyl in dosages of 50–100 μg/kg releases little histamine and provides a hemodynamically acceptable anesthetic. Sufentanil, 15–25 μg/kg, has been said not only to provide as stable an induction as fentanyl, but also potentially to add further protection from intraoperative hypertension and tachycardia, and to produce less postoperative respiratory depression (2).

The following clinical report describes four patients in whom sudden hypotension developed on induction of anesthesia with sufentanil ranging in dose from 8.4 μg/kg to 22.7 μg/kg. Three patients were having cardiac surgery: coronary artery bypass graft (CABG) in one, mitral valve replacement (MVR) in one, and combined MVR and CABG in the third. The fourth patient was scheduled for resection of an abdominal aortic aneurysm (AAA). At this time ten cases of high-dose sufentanil anesthesia have been carried out at this institution, including the four reported here.

Case 1

A 50-yr-old man weighing 95 kg with a history of hypertension, two myocardial infarctions within the last year, and unstable angina was scheduled for combined MVR and CABG. His medications included procainamide, 500 mg every 6 hr, furosemide, 40 mg twice a day, digoxin, 0.25 mg every morning, nitroglycerin tablets sublinguially as necessary, nitroglycerin patch every 12 hr, and an oral potassium supplement. Cardiac catheterization showed triple vessel coronary artery disease and moderate mitral regurgitation with a left ventricular end diastolic pressure of 26 torr.

The patient was premedicated with morphine, 10 mg, and glycopyrrolate, 0.2 mg intramuscularly. He was further sedated with 3 mg of intravenous lorazepam while an arterial line and a Swan–Ganz introducer sheath were placed.

Anesthesia was induced with an infusion of 10 μg/ml of sufentanil by slow infusion. Blood pressure was 140/80 torr and pulse 74 beats/min. Ten minutes after the infusion was begun, the blood pressure decreased to 60/40 torr with no change in pulse. A dose of 8.4 μg/kg sufentanil had been infused when it was stopped and the trachea intubated, without change in the vital signs. Five hundred milliliters of lactated Ringer's solution administered rapidly and bolus intravenous injections of ephedrine (10 mg) increased the blood pressure to 170/110 torr 4 min after the onset of hypotension. The pulse rate remained at 75–80 beats/min. Upon Swan–Ganz catheter insertion, a pulmonary capillary occlusion pressure of 27 torr, a cardiac index of 1.8 $L{\cdot}min^{-1}{\cdot}m^{-2}$, and a systemic vascular resistance of 1476 $dynes{\cdot}sec{\cdot}cm^{-5}$ were recorded.

Case 2

A 72-yr-old woman weighing 55 kg was scheduled for mitral valve replacement. The patient had a history of dyspnea, congestive failure, and a previous cerebral infarction. Her only medication was digoxin, 0.125 mg each morning. Cardiac catheterization showed mitral stenosis with a valve area of 0.5 cm^2 and a 23 torr gradient, and a cardiac output of 4.5 L/min. Left ventricular end diastolic pressure was 3 torr, and the pulmonary artery pressure was 68/31 torr with an occlusion pressure of 29 torr.

The patient was given morphine, 8 mg, and glycopyrrolate, 0.2 mg, intramuscularly before the operation. Further sedation with lorazepam (2 mg) was

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Address correspondence to Dr. Spiess, Department of Anesthesiology, Rush Presbyterian St. Luke's Medical Center, Chicago, IL 60612.

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added during placement of monitors. Vital signs preoperatively were the following: blood pressure, 130/70 torr; pulse 70 beats/min; and central venous pressure, 17 torr.

Anesthesia was induced with 25 ml (50 μg/ml) of sufentanil carried out over 10 min (22.7 μg/kg). The blood pressure decreased to 60/40 torr with a pulse of 65 in the 5 min after the completion of the infusion. Intubation did not change the vital signs. Lactated Ringer's solution (500 ml) plus incremental intravenous doses of phenylephrine (400 μg in 100 μg increments) restored the blood pressure to 120/65 torr and the pulse to 80 beats/min in 3 min.

Case 3

A 42-yr-old man weighing 90 kg with a history of unstable angina, hypertension, and two previous myocardial infarctions was scheduled for CABG. His medications included propranolol, nitroglycerin patch, and verapamil. The electrocardiogram showed normal sinus rhythm with Q waves in leads II, III, and aV_F. Cardiac catheterization showed severe three-vessel coronary artery disease, left ventricular hypokinesis, and elevated left ventricular end diastolic pressures.

The patient was premedicated with morphine 10 mg and 0.2 mg of glycopyrrolate. Lorazepam, 4 mg, was intravenously given for further sedation during placement of intravenous, arterial, and central lines. One milliliter (50 μg/ml) of sufentanil was followed 2 min later with another 4 ml. The pulse rate decreased from 80 to 48 beats/min and the blood pressure from 130/70 to 60/30 torr. Immediate intubation did not change the vital signs. Atropine (1.2 mg), ephedrine (20 mg) and epinephrine (200 μg) were given in divided doses. The patient's blood pressure slowly increased to 200/110 torr with a pulse of 85 beats/min over the following 5 min. A Swan–Ganz thermodilution catheter inserted after resuscitation showed a pulmonary occlusion pressure of 21 torr, cardiac output of 3.34 liters/min, cardiac index of 1.67 $L{\cdot}min^{-1}{\cdot}m^{-2}$ and a systemic vascular resistance of 2035 dynes-sec-cm^{-5}.

Case 4

A 90kg 72-yr-old man with a history of well-controlled hypertension and previous cerebral vascular accident was scheduled for an AAA. The patient's medications were cimetidine and hydrochlorothiazide.

Preoperative medication consisted of lorazepam, 2 mg, and atropine, 0.4 mg intramuscularly. One milliliter of sufentanil (50 μg/ml) was given as a test dose followed by 4 more ml over 3 min. The blood pressure decreased from 180/90 torr to 88/60 torr and the pulse from 88 to 64 beats/min. Immediate intubation did not change the vital signs. Atropine, 0.4 mg, increased the pulse rate to 80 beats/min and the blood pressure to 110/70 torr. Central venous pressure prior to induction was 12 torr. A Swan–Ganz catheter was later placed and revealed normal cardiac output, cardiac index and pulmonary capillary occlusion pressure.

Discussion

Sufentanil is a synthetic opiate 5–10 times more potent than fentanyl. Intraoperative prevention of hypertension and tachycardia, and decreased postoperative respiratory depression have been proposed as advantages over fentanyl (3,4). These would truly be advances in cardiac anesthesia if sufentanil has as little cardiovascular effect during induction as fentanyl. Sufentanil and fentanyl are comparable in both induction time and cardiovascular stability in CABG patients. Mean arterial pressure, heart rate, pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac index, peripheral resistance, and pulmonary vascular resistance all remain unchanged during induction of anesthesia with sufentanil (2,3,5,6). However, our study reported significant decreases in cardiac contractility on induction with sufentanil leading to a decrease in mean arterial pressure (6). Cardiovascular changes during induction with sufentanil in patients undergoing mitral valve replacement include decreases in mean arterial blood pressure (−24.5 torr) and systemic vascular resistance (6). Patients with low cardiac output and high pulmonary capillary occlusion pressures do not routinely have pronounced decreases in blood pressure during induction to anesthesia with sufentanil (6). Two cases reported here underwent mitral valve replacements with major (70 torr) decreases in mean arterial pressures after sufentanil administration.

Histamine release has caused problems with other opiates, notably morphine. However, histamine release is not a problem during induction with high dose sufentanil (7,8,9). There was no evidence to support histamine as a mediator of the hypotensive responses in the present four cases.

Decreases in serum levels of epinephrine and norepinephrine have been described in patients anesthetized with high dose sufentanil (10). The rate of infusion may contribute to changes in catecholamine levels. Cases 3 and 4 had very slow inductions with small amounts of sufentanil in test doses; two cases (cases 1 and 2) received their sufentanil over 5–10 min with one patient receiving 22.7 μg/kg over 10 min.

More studies of catecholamine levels following induction with high-dose sufentanil are needed.

Increased vagal tone is a well-described side effect of high-dose sufentanil and fentanyl anesthesia (2). Cases 3 and 4 had decreases in pulse rate greater than 25%. Those bradycardias may have been a factor decreasing cardiac output in these two patients.

All four patients received lorazepam 2–5 mg at least 30 min prior to induction. Benzodiazepine–opiate combinations have been shown to cause hypotension and decreased cardiac output. Diazepam–morphine or diazepam–fentanyl combinations, for example, decrease heart rate and mean arterial pressure, and increase peripheral vascular resistance (11,12). Although lorazepam as a pretreatment to high-dose fentanyl anesthesia has no major cardiovascular effects (13), diazepam–sufentanil as a combination has been associated with direct myocardial depression and a decrease in preload. No data have been gathered on cardiovascular responses to lorazepam–sufentanil combinations. Cardiovascular depression with the lorazepam–sufentanil combination may have been the major contributor to the hypotension in these cases.

Thoracic muscular rigidity occurs with both fentanyl and sufentanil (3). Increased intrathoracic pressures caused by such rigidity could decrease venous return and cardiac output. There was no evidence of ventilatory difficulty in any of the four cases reviewed.

In summary, four of the ten cases in which sufentanil was used for induction of anesthesia developed sudden hypotension. Each of the four cases had pretreatment with lorazepam. Three of these cases were scheduled for open heart surgery, and one case was scheduled for resection of an abdominal aneurysm. The mechanisms for the sudden hypotensive episodes are unclear, and invasive monitoring was not performed during the hypotensive episodes. Possible mechanisms include a sudden decrease in circulating catecholamines, increased vagal tone, relative overdosage with a very potent agent, and a benzodiazepine–narcotic interaction.

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Use of Nicardipine in the Anesthetic Management of Pheochromocytoma

Toshiyuki Arai, MD, Yoshio Hatano, MD, PhD, Hiroyuki Ishida, MD, and Kenjiro Mori, MD, PhD

For the operative management of pheochromocytoma, phentolamine or sodium nitroprusside have been commonly used for prevention of dangerous hypertension caused by catecholamine release from the tumor. However, these agents exhibit antihypertensive properties by acting on vascular smooth muscle (1,2), not by inhibiting catecholamine release. Recently, the clinical benefits of nifedipine, a calcium slow-channel blocker (i.e., Ca antagonist), have been confirmed in the management of pheochromocytoma symptoms such as acute hypertensive crisis, cardiomyopathy, angina, and palpitation (3,4). Serfas et al. have suggested that the effectiveness of calcium antagonists is related both to its potent vasodilating action and to partial suppression of catecholamine release from pheochromocytoma (4). We report a case of pheochromocytoma successfully managed intraoperatively with an infusion of nicardipine, a new short-acting calcium antagonist for intravenous use, in a patient in whom sublingual administration of nifedipine had been effective for relief of the preoperative symptoms.

Case Report

A 42-yr-old woman, weighing 47 kg, with a 1-yr history of severe headaches was admitted to the hospital because of marked hypertension. The presence of an adrenal pheochromocytoma was confirmed by angiography and by the findings of elevated levels of serum catecholamines and urinary vanillylmandelic acid, and she was scheduled to have the pheochromocytoma excised. On admission, her blood pressure was 242/108 mm Hg and her heart rate was 110 beats/min with normal sinus rhythm. Serum norepinephrine and epinephrine levels were 45,500 pg/ml (normal, 40–350) and 104 pg/ml (normal, <120), respectively. Other laboratory data were within normal limits. Medication consisting of prazocin (2 mg) and metoprolol (40 mg) orally three times daily was continued for 4 weeks until the day before the operation. A few days after the start of medication, the patient's blood pressure decreased to a range of 190/100–170/90 mm Hg, but she continued to have episodes of severe headache, and hypertension as high as 240/140 mm Hg. On one occasion, sublingual administration of nifedipine (10 mg) was effective in relieving her headache and lowering her blood pressure from 254/145 to 120/80 mm Hg within 10 min, in association with an abrupt decrease in serum catecholamine levels. Serum levels of norepinephrine and epinephrine during this hypertensive attack were 92,800 pg/ml and 340 pg/ml, and, 10 min after nifedipine administration, 43,200 and 240 pg/ml, respectively. Thereafter, nifedipine was prescribed when these episodes occurred.

The patient was premedicated with 10 mg diazepam given orally 1 hr before induction of anesthesia, and with 0.4 mg scopolamine and 10 mg morphine given intramuscularly 30 min before induction. On arrival in the operating room, she appeared to be well-sedated; arterial blood pressure was 190/120 mm Hg and heart rate 106 beats/min. The right radial artery was cannulated under local anesthesia. A Swan–Ganz catheter (7F, American Edwards Lab.) was inserted via the right internal jugular vein under local anesthesia. Cardiovascular profiles were measured, and an arterial blood specimen was obtained for measurement of serum catecholamine concentrations by means of high-performance liquid chromatography (Table 1).

Anesthesia was then induced with 10 mg diazepam, which decreased the patient's blood pressure to 170/100 mm Hg, followed by infusion of fentanyl (50 μg/kg) at a rate of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. After 1 mg of fentanyl had been infused, the blood pressure increased to 260/150 mm Hg and heart rate from 95 to

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Address correspondence to Dr. Hatano, Department of Anesthesiology, Kyoto University Hospital, Sakyo-ku, Kyoto 606, Japan.

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Table 1. Hemodynamic Parameters and Plasma Catecholamine Levels before, during, and after Resection of Pheochromocytoma

	Blood pressure (mm Hg)	Heart rate (beats/min)	Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	Systemic vascular resistance dyne-sec/cm^5	Norepinephrine[a] pg/ml	Epinephrine[b] pg/ml
Before induction	193/105	110	2.56	2,990	97,800	302
After intubation	120/70	105	—	—	33,900	70
Exploration of abdomen	145/85	88	3.74	1740	36,300	30
Manipulation of the tumor	134/77	110	5.14	1040	51,200	30
After resection	80/55	96	2.99	1070	3150	28
After operation	130/80	100	3.84	1370	5070	378
1 week after operation	138/95	92	—	—	550	23

[a] Normal values, 40–350 pg/ml.
[b] Normal values, <120 pg/ml.

130 beats/min. Nicardipine infusion was immediately started at a rate of 2 mg/min for 90 sec, after which the blood pressure decreased to 125/75 mm Hg; heart rate was 110 beats/min. The trachea was then intubated after administration of 6 mg of pancuronium. Cardiovascular response to endotracheal intubation was minor. Anesthesia was maintained with 50% nitrous oxide in oxygen and with intermittent doses of pancuronium as required. During exploration of the abdomen, the blood pressure remained in a range of 120/80–145/90 mm Hg with the nicardipine infusion (0.1–0.2 mg/min). Extensive manipulation of the pheochromocytoma elevated the pressure to 180/110 mm Hg. However, this elevation responded immediately to an increase in the rate of nicardipine infusion (1 mg/min). The heart rate during surgery remained relatively stable in the range of 88–120 beats/min with normal sinus rhythm. After the removal of the tumor, nicardipine infusion was discontinued, and the blood pressure gradually decreased to 80/55 mm Hg and heart rate to 100 beats/min. Blood pressure increased to 120/80 mm Hg within 60 min after blood transfusion and fluid therapy. After the operation, the patient was transferred to the intensive care unit; no vasopressor therapy was required. Twenty hours after operation, the patient was extubated after acceptable respiratory and hemodynamic findings were obtained. The patient was discharged 26 days after the operation without any complications.

Discussion

Transmembrane Ca^{2+} influx initiated by depolarization of the cell membrane is necessary for catecholamine release from adrenal medullary tissue (5), as well as for the contraction of blood vessels and heart (6). Calcium antagonists, in addition to their effects on the cardiovascular system, also inhibit catecholamine release by the adrenal medulla (7,8). In our patient, administration of nifedipine effectively controlled preoperative hypertensive attacks and headaches, and was associated with abrupt decreases in plasma catecholamine levels. During the operation nicardipine infusion maintained the catecholamine levels below the preoperative level, even during manipulation of the tumor. Sudden increases in plasma catecholamine levels during tracheal intubation or operative manipulation of the tumor, which have been reported in patients with pheochromocytomas even when adequate blood pressure was maintained using phentolamine or sodium nitroprusside (9–11), did not occur when we used the infusion of nicardipine. Although the response of catecholamine release from pheochromocytoma to calcium antagonists has not yet been defined, our observation suggests that nicardipine is valuable for prevention of excess catecholamine release during resection of pheochromocytomas. In addition to adequate blood pressure control, the cardiac index was well-preserved and systemic vascular resistance remained within normal limits despite the presence of elevated circulating catecholamine levels. Nicardipine has been shown to have greater effects on the peripheral vessels than on the heart in healthy volunteers (12) and in anesthetized patients who develop acute hypertension (13). Although severe tachyarrhythmias can occur during surgery, the heart rate of our patient changed little, probably because of the negative chronotropic action of nicardipine (14) and the suppression of catecholamine release by nicardipine infusion. In addition, because of the short duration of action of nicardipine (12,13), the blood pressure after removal of the pheochromocytoma could be maintained adequately with conventional fluid therapy.

In our patient, anesthesia was induced with high-dose fentanyl because this has been reported to prevent surgically-induced increases in plasma catecholamines (15) and to possess postsynaptic α-adrenergic blocking action (16). However, infusion of fentanyl elicited marked hypertension, which was reversed by infusion of nicardipine. This hypertension may have been related to the effects of fentanyl on adrenergic nerve endings, facilitation of norepinephrine release (17), and inhibition of neural norepinephrine uptake (18). Increased serum norepinephrine levels have been reported during induction with high-dose fentanyl in patients with ischemic heart disease (19).

In summary, the use of nicardipine, a short-acting calcium antagonist, provided adequate hemodynamic control in association with lowered catecholamine levels during removal of pheochromocytoma. Nicardipine could be useful in the anesthetic management of patients undergoing surgery for pheochromocytoma.

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Book Reviews

1985 Yearbook of Anesthesia

Ronald D. Miller, Robert R. Kirby, Gerald W. Ostheimer, Lawrence J. Saidman, and Robert K. Stoelting, eds.
Chicago: Yearbook Medical Publishers, Inc., 1985, 395 pp.

1985 is the twenty-second year for the Yearbook Medical Publishers' *Yearbook of Anesthesia* series. This year's format remains the same as in previous years. Drs. Miller, Kirby, Ostheimer, Saidman, and Stoelting have reviewed over 300 articles and case reports selected from the world's relevant anesthesia literature. These are ranged under 13 chapter headings beginning with an introductory chapter entitled "The Informed Anesthesiologist," and then continuing with extensive sections devoted to areas such as pharmacology, anesthesia for different types of surgery, postoperative care, ventilatory management, and critical care. Articles are summarized and receive editorial comment, which may vary from scholarly critiques to a few humorous bon mots. (All the cited articles are not necessarily landmark studies, and examples of poor scholarship are occasionally included with appropriate criticism).

The publisher introduces the reader to this year's new cover design and content format. The latter is a great improvement. The new typeset and citation headings make the 1985 issue much easier to read than its predecessors. Each page has a nice sense of balance. Hopefully, tiny editorial type, run-on summaries, and poorly identified headings are gone forever.

Even though the 1985 *Yearbook* is a continuation of the yearbook series, it should be able to stand alone to be a success. It should be topical and mirror the controversies and consensus of the specialty for its year. The *Yearbook* covers the reviewed anesthesia literature from November 1983 until October 1984 extremely well. Topics such as aspiration pneumonia are covered in great detail. Samples of the relevant literature dealing with histamine antagonists, antacids, and metoclopramide are clearly presented. Likewise, the literature reviews for transfusions, obstetrical anesthesia, and spinal opioids are well-balanced and highly recommended. Pediatric anesthesia was extensively covered by the 1984 yearbook, but, unfortunately, 1985 includes only a few citations which are scattered throughout the book and are not well cross-referenced. I occasionally had difficulty finding what I wanted. For example, articles that dealt with deliberate hypotension and adenosine could be found in both the chapter "Anesthetic Techniques" and again in the chapter "Anesthesia for Certain Types of Surgery." Finally, I was disappointed that there were no articles dealing with two-dimensional echocardiography or its operating room applications.

In summary, I believe that the editors and publishers of the *Yearbook* series have produced a concise and expertly executed synopsis of the anesthesia literature. Clearly, it should not be a substitute for the original articles, nor should it be thought to be a definitive review of the literature. It does offer the busy practitioner or trainee a widened perspective with which to view our specialty. I recommend the *1985 Yearbook of Anesthesia* to everyone who might benefit from this widened perspective.

Mark M. Harris, MD
Assistant Professor of Anesthesiology
University of Virginia Medical Center
Charlottesville, VA 22908

International Anesthesiology Clinics: Special Problems in Pediatric Anesthesia

Rodolfo I. Godinez, ed. Boston: Little Brown and Company, 1985, 235 pp, $24.00.

The overwhelming volume of information produced in recent years in the area of pediatric anesthesia has prevented the production of a single, authoritative text to cover the specialty. Despite attempts, no book has succeeded the "Smith Classic," and it is doubtful if such could be produced. In its place, we must look to shorter, directed works such as this fine volume of *International Anesthesiology Clinics*. Dr. Godinez has assembled a review of current philosophies and practies representing the CHOP (Children's Hospital of Philadelphia) view of pediatric anesthesia practice. This is a conservative, widely respected, and well-tested approach to the care of children. In presenting their views, the individual authors have been careful to avoid rigidity and to champion the safety of children. The chapters are well-chosen to cover the field of common interests, and readers are helped by useful names of less common equipment and their manufacturers.

Perhaps the best quality of the work is the excellent reference list provided by each set of authors, which should prove to be a standard reference list of all levels of readership. The style of presentation is most conducive to easy reading and, apart from occasional minor errors (fluids chart, page 143) and some unavoidable repetition, this volume could become the most popular pediatric anesthesia reference in recent times.

The chapters on preanesthetic considerations by Broennle and airway surgery by Keon should prove especially valuable, whereas those on craniofacial surgery and transplantation carry sufficient depth to remind the overconfident that the pediatric anesthesia care team has attained a great deal of sophistication. The text further reminds us that the occasional pediatric encounter needs to be approached with extreme caution, and provides much encouragement to those who judge that a particular level of care is the maximum their facility should provide.

I would consider this a "must" companion to Steward's *Handbook* for all who do not restrict their practice to children, and I recommend it strongly for those who do.

Eric B. Furman, MD
Director
Department of Anesthesiology
Children's Orthopedic Hospital and Medical Center and
University of Washington
Seattle, WA 98105

Books Received

Receipt of the following books from their publishers is acknowledged with thanks. Selected books from this list will be reviewed in the future.

Anaesthetic Management, A Rule-Based Guide. M. J. Harrison, R. M. Jones, B. J. Pollard. Stoneham, MA: Butterworth, 1986, 283 pp, $29.95.

Anesthesia in Obstetrics: Maternal, Fetal, and Neonatal Aspects. G. A. Albright, J. E. Ferguson II, T. H. Joyce III, D. K. Stevenson. Stoneham, MA: Butterworth, 1986, 662 pp, $69.96.

Basic Physics and Measurement in Anesthesia. G. D. Parbrook, P. D. Davis, E. O. Parbrook. E. Norwalk, CT: Appleton-Century Crofts, 1985, 360 pp, $34.95.

Cardiac Catheterization and Angiography, third edition. W. Grossman, ed. Philadelphia: Lea & Febiger, 1986, 562 pp, $49.50.

Computers in Critical Care and Pulmonary Medicine. P. M. Osswald, ed. NY: Springer-Verlag, 1985, 340 pp, $44.70.

The Heart: Physiology, Metabolism, Pharmacology, Therapy. L. Opie, ed. Orlando, FL: Grune & Stratton, 1984, 392 pp, $55.00.

Isoflurane (Forane), second edition. E. I. Eger II. Madison, WI: Anaquest, 1986, 160 pp.

The Management of Postoperative Pain. M. E. Dodson. Baltimore: Arnold, 1985, 274 pp, $49.95.

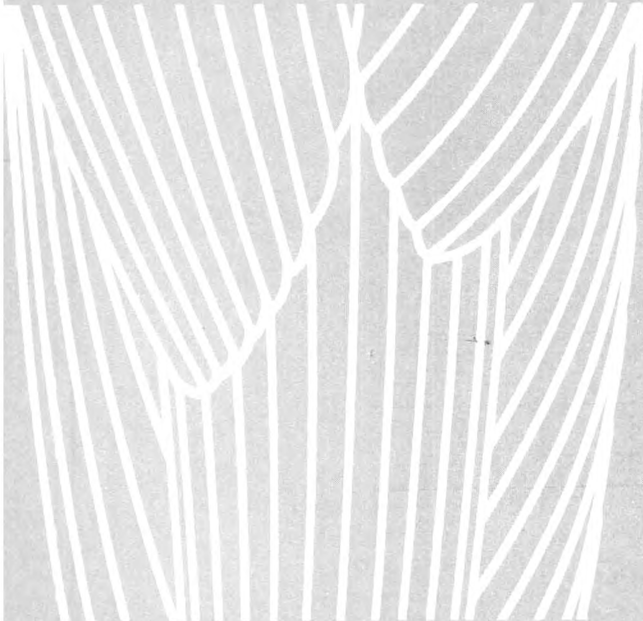
Mises au Point en Anesthesie—Reanimation. Y. Noviant, J. Langloys. Le Kremlin-Bicêtre, France: MAPAR, 1985, 474 pp, $29.10.

Muscle Relaxants: Basic and Clinical Aspects. R. L. Katz, ed. Orlando, FL: Grune & Stratton, 1985, 305 pp, $24.40.

A Primer of Water, Electrolyte, and Acid–Base Syndromes, seventh edition. E. Goldberger, J. M. Brensilov. Philadelphia: Lea & Febiger, 1986, 414 pp, $19.50.

Review of Allied Health Education: 4. J. Hamburg, D. J. Mase, W. S. Perry, eds. Lexington, KY: University of Kentucky Press, 1981, 148 pp, $16.00.

Review of Allied Health Education: 5. J. Hamburg, D. J. Mase, W. S. Perry, eds. Lexington, KY: University of Kentucky Press, 1985, 165 pp, $16.00.



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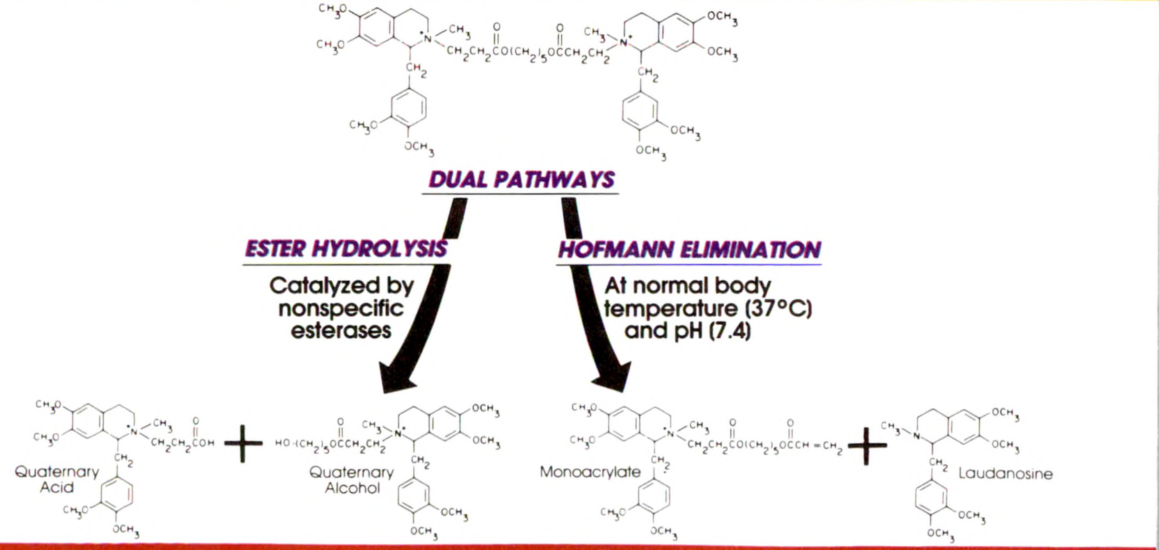

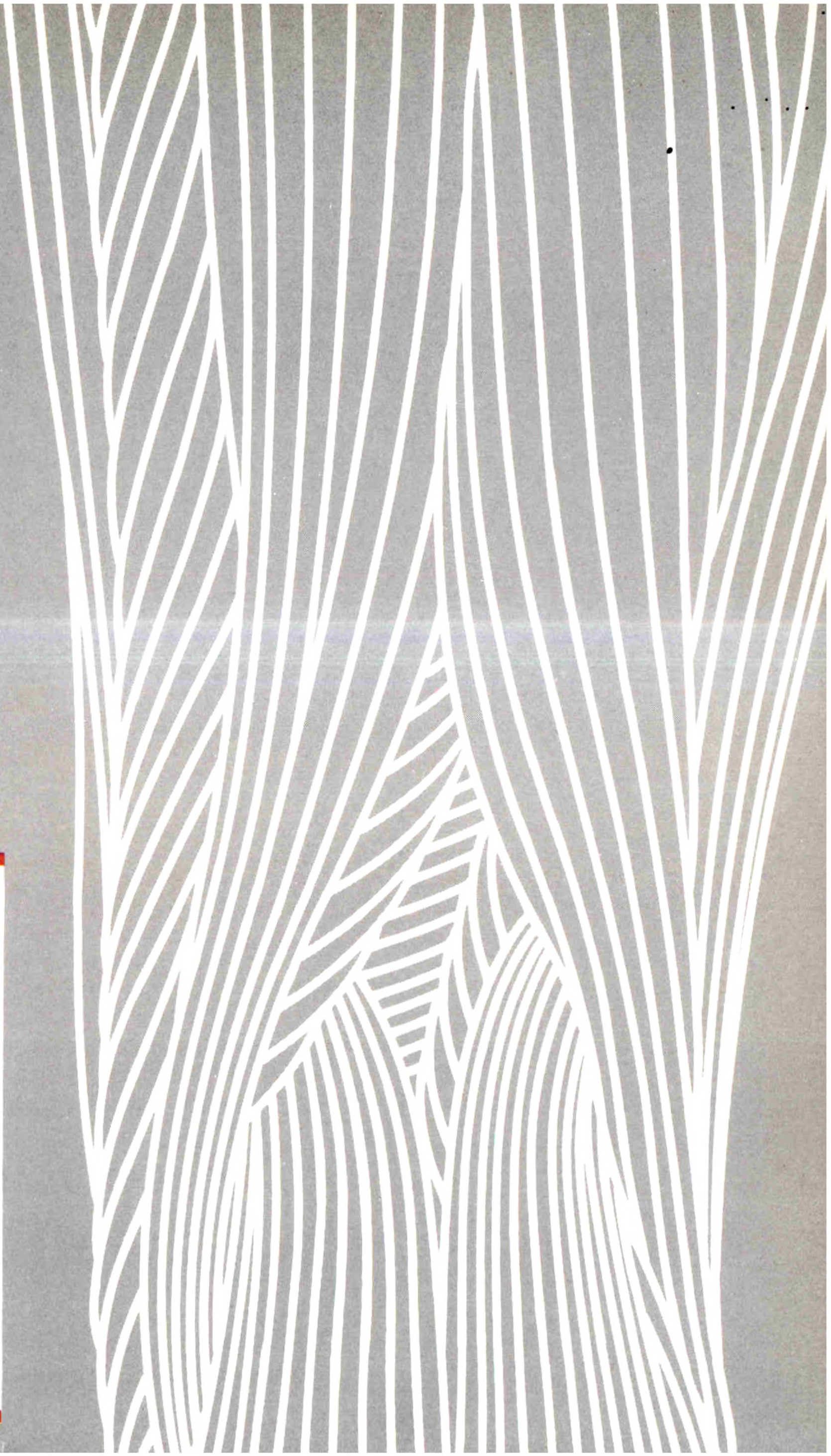

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Reference:
1. Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, and d-tubocurarine, abstracted. Anesthesiology 1982;57:A261.

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CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

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Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

PRECAUTIONS:
General: Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

Drug Interactions: The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. Atracurium was evaluated in a battery of three short term mutagenicity tests. It was non-mutagenic in both the Ames Salmonella assay at concentrations up to 1000 μg/plate, and in a rat bone marrow cytogenicity assay at up to paralyzing doses. A positive response was observed in the mouse lymphoma assay under conditions (80 and 100 μg/ml, in the absence of metabolic activation) which killed over 80% of the treated cells; there was no mutagenicity at 60 μg/ml and lower, concentrations which killed up to half of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations (1200 μg/ml and higher) which also killed over 80% of the treated cells. Mutagenicity testing is intended to simulate chronic (years to lifetime) exposure in an effort to determine potential carcinogenicity. Thus, a single positive mutagenicity response for a drug used infrequently and/or briefly is of questionable clinical relevance.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

Approximately one million patients received Tracrium during the first year following introduction to the U.S. market in December, 1983. Spontaneously reported adverse reactions were uncommon (approximately 0.02%). The following adverse reactions are among those most frequently reported, but there are insufficient data to support an estimate of their incidence:
Musculoskeletal: Inadequate block, prolonged block
Cardiovascular: Hypotension, vasodilatation (flushing), tachycardia, bradycardia
Respiratory: Dyspnea, bronchospasm, laryngospasm
Integumentary: Rash, urticaria, reaction at injection site

DOSAGE AND ADMINISTRATION: Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Adults: A Tracrium dose of 0.4 to 0.5 mg/kg (1.7-2.2 times the ED_{95}), given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

Children and Infants: No Tracrium dosage adjustments are required for pediatric patients two years of age or older. A Tracrium dose of 0.3 to 0.4 mg/kg is recommended as the initial dose for infants (1 month to 2 years of age) under halothane anesthesia. Maintenance doses may be required with slightly greater frequency in infants and children than in adults.

Special Considerations: An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for adults, children, or infants with significant cardiovascular disease and for adults, children, or infants with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated. No Tracrium dosage adjustments are required for patients with renal disease.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended for adults following the use of succinylcholine for intubation under balanced anesthesia. Further reductions may be desirable with the use of potent inhalation anesthetics. The patient should be permitted to recover from the effects of succinylcholine prior to Tracrium administration. Insufficient data are available for recommendation of a specific initial Tracrium dose for administration following the use of succinylcholine in children and infants.

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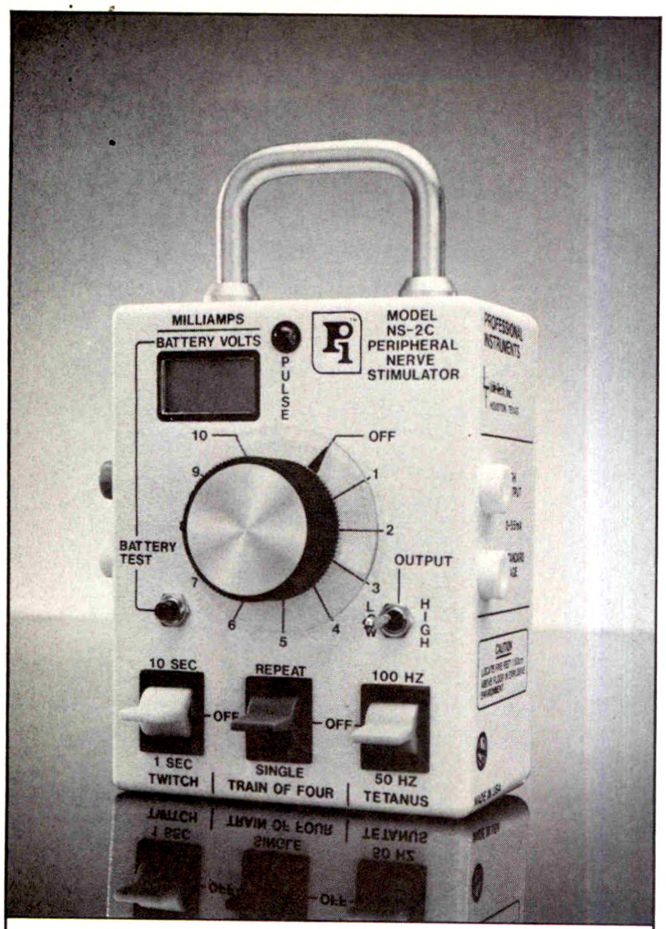

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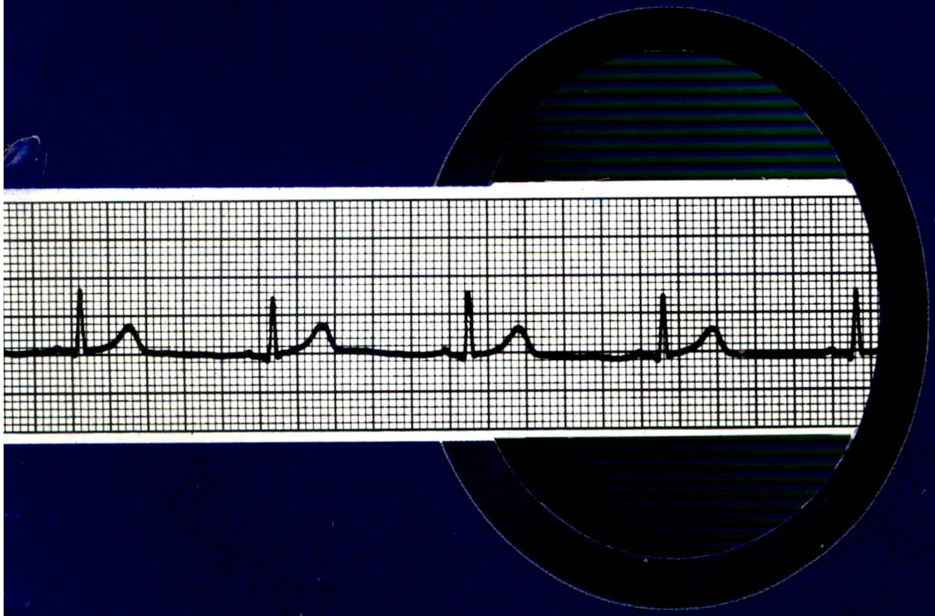
Heart failure
patients are often
at risk of
arrhythmias...



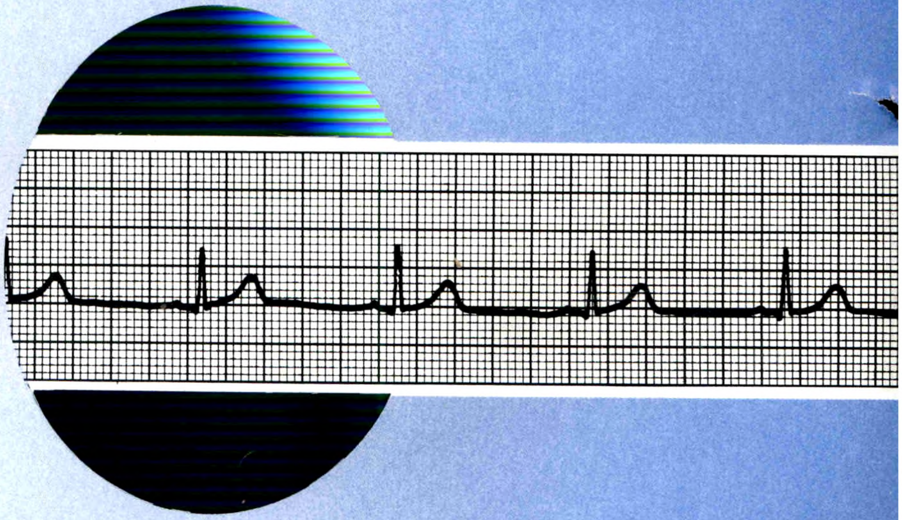
Now...
an inotropic agent
that does not significantly
increase heart rate

energy efficient

Inocor® I.V.

(AMRINONE)

Rapidly increases cardiac output with minimal effect on heart rate or rhythm



- ○ Substantially improves contractility without adding to myocardial oxygen demand
- ○ Lowers pulmonary capillary wedge pressure and systemic vascular resistance
- ○ Heart rate and blood pressure virtually unchanged
- ○ INOCOR is intended for short-term use in patients who can be closely monitored and do not respond adequately to prior treatment with digitalis, diuretics, and/or vasodilators.

*For important product information concerning contraindications, adverse reactions, patient selection, and precautionary recommendations, please see last page.

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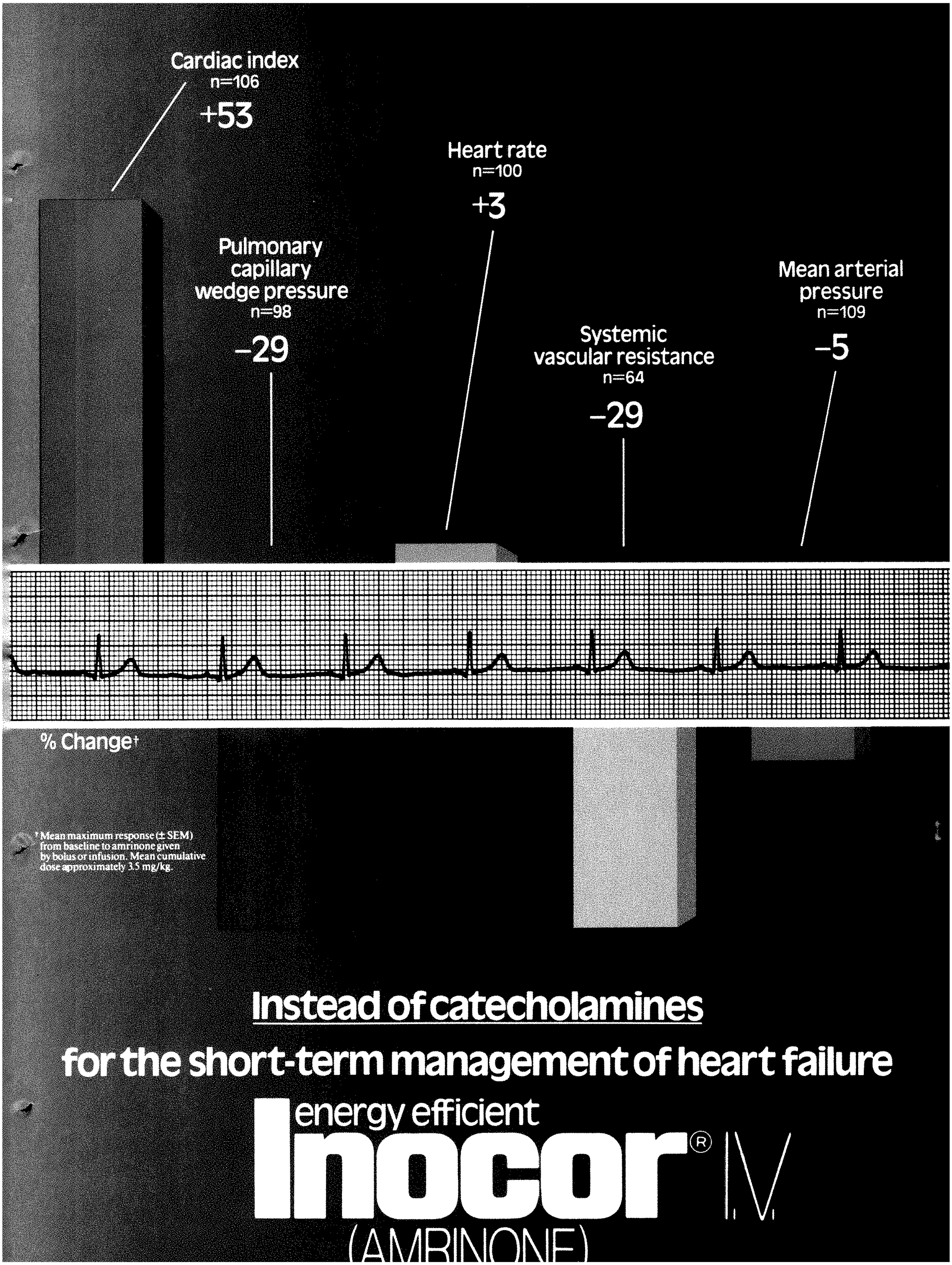


† Mean maximum response (± SEM) from baseline to amrinone given by bolus or infusion. Mean cumulative dose approximately 3.5 mg/kg.

Instead of catecholamines

for the short-term management of heart failure

energy efficient

Inocor® I.V.

(AMRINONE)

A major advance toward better inotropic therapy

energy efficient
Inocor® I.V.
(AMRINONE)

Instead of catecholamines for the short-term management of heart failure

- Independent of the effects of digitalis and catecholamines
- Hemodynamics rapidly improved
- Heart rate and blood pressure not significantly changed… has not been shown to increase risk of arrhythmias (see precautions)
- Can be used in patients with myocardial ischemia
- Benefits sustained during therapy… no evidence of tachyphylaxis
- Easy to administer

Patients receiving INOCOR should be carefully monitored with the following laboratory studies: platelet counts, liver enzymes, fluid and electrolyte changes, and renal function. Hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use.

Please see brief summary of product information on this page for contraindications, adverse reactions, patient selection, and precautionary recommendations.

Winthrop-Breon

Winthrop-Breon Laboratories, Division of Sterling Drug Inc. New York, NY 10016

INOCOR lactate injection, brand of amrinone lactate, represents a new class of cardiac inotropic agents with vasodilator activity, distinct from digitalis glycosides or catecholamines.

INDICATIONS AND USAGE (INOCOR lactate injection is indicated for the short-term management of congestive heart failure in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators.)

INOCOR lactate injection is indicated for the short-term management of congestive heart failure. Because of limited experience and potential for serious adverse effects (see ADVERSE REACTIONS), INOCOR should be used only in patients who can be closely monitored and who have not responded adequately to digitalis, diuretics, and/or vasodilators. Although most patients have been studied hemodynamically for periods only up to 24 hours, some patients were studied for longer periods and demonstrated consistent hemodynamic and clinical effects. The duration of therapy should depend on patient responsiveness

CONTRAINDICATIONS INOCOR lactate injection is contraindicated in patients who are hypersensitive to it.

It is also contraindicated in those patients known to be hypersensitive to bisulfites

PRECAUTIONS *General:* INOCOR lactate injection should not be used in patients with severe aortic or pulmonic valvular disease in lieu of surgical relief of the obstruction. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

During intravenous therapy with INOCOR lactate injection, blood pressure and heart rate should be monitored and the rate of infusion slowed or stopped in patients showing excessive decreases in blood pressure

Patients who have received vigorous diuretic therapy may have insufficient cardiac filling pressure to respond adequately to INOCOR lactate injection, in which case cautious liberalization of fluid and electrolyte intake may be indicated

Supraventricular and ventricular arrhythmias have been observed in the very high-risk population treated. While amrinone per se has not been shown to be arrhythmogenic, the potential for arrhythmia, present in congestive heart failure itself may be increased by any drug or combination of drugs.

Thrombocytopenia and hepatotoxicity have been noted (see ADVERSE REACTIONS).

LABORATORY TESTS *Fluid and electrolytes:* Fluid and electrolyte changes and renal function should be carefully monitored during amrinone lactate therapy Improvement in cardiac output with resultant diuresis may necessitate a reduction in the dose of diuretic. Potassium loss due to excessive diuresis may predispose digitalized patients to arrhythmias. Therefore, hypokalemia should be corrected by potassium supplementation in advance of or during amrinone use

DRUG INTERACTIONS In a relatively limited experience, no untoward clinical manifestations have been observed in patients in whom INOCOR lactate injection was used concurrently with the following drugs: digitalis glycosides, lidocaine, quinidine, metoprolol, propranolol; hydralazine, prazosin, isosorbide dinitrate, nitroglycerine, chlorthalidone, ethacrynic acid, furosemide, hydrochlorothiazide, spironolactone, captopril, heparin, warfarin, potassium supplements, insulin, diazepam

One case of excessive hypotension was reported when amrinone was used concurrently with disopyramide.

Until additional experience is available, concurrent administration with Norpace® disopyramide should be undertaken with caution

USE IN ACUTE MYOCARDIAL INFARCTION INOCOR is not recommended for use in acute myocardial infarction.

USE IN CHILDREN Safety and effectiveness in children have not been established

USE IN PREGNANCY *Pregnancy category C* In New Zealand white rabbits, amrinone has been shown to reduce fetal skeletal and gross external malformations at oral doses of 16 mg/kg and 50 mg/kg that were toxic for the rabbit. Studies in French Hy/Cr rabbits using oral doses up to 32 mg/kg/day did not confirm this finding. No malformations were seen in rats receiving amrinone intravenously at the maximum dose used, 15 mg/kg/day (approximately the recommended daily IV dose for patients with congestive heart failure) There are no adequate and well-controlled studies in pregnant women. Amrinone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

USE IN NURSING MOTHERS Caution should be exercised when amrinone is administered to nursing women, since it is not known whether it is excreted in human milk.

ADVERSE REACTIONS *Thrombocytopenia* Intravenous INOCOR lactate injection resulted in platelet count reductions to below 100,000/mm^3 in 2.4% of patients.

Gastrointestinal effects: Gastrointestinal adverse reactions reported with INOCOR lactate injection during clinical use included nausea (1.7%), vomiting (0.9%), abdominal pain (0.4%), and anorexia (0.4%).

Cardiovascular effects Cardiovascular adverse reactions reported with INOCOR lactate injection include arrhythmia (3%) and hypotension (1.3%)

Hepatic toxicity: in dogs, at IV doses between 9 mg/kg/day and 32 mg/kg/day, amrinone showed dose-related hepatotoxicity manifested either as enzyme elevation or hepatic cell necrosis or both. Hepatotoxicity has been observed in man following long-term oral dosing and has been observed, in a limited experience (0.2%), following IV administration of amrinone

Hypersensitivity There have been reports of several apparent hypersensitivity reactions in patients treated with oral amrinone for about two weeks. Signs and symptoms were variable but included pericarditis, pleuritis, and ascites (one case), myositis with interstitial shadowing on chest x-ray and elevated sedimentation rate (one case), and vasculitis with nodular pulmonary densities, hypoxemia, and jaundice (one case) The first patient died, not necessarily of the possible reaction, while the last two resolved with discontinuation of therapy. None of the cases were rechallenged, so attribution to amrinone is not certain, but possible hypersensitivity reactions should be considered in any patient maintained for a prolonged period on amrinone

General: Additional adverse reactions observed in intravenous amrinone clinical studies include fever (0.9%), chest pain (0.2%), and burning at the site of injection (0.2%).

OVERDOSAGE Doses of INOCOR lactate injection may produce hypotension because of its vasodilator effect. If this occurs, amrinone administration should be reduced or discontinued. No specific antidote is known, but general measures for circulatory support should be taken

MANAGEMENT OF ADVERSE REACTIONS *Platelet count reductions* Asymptomatic platelet count reduction (to less than 150,000/mm^3) may be reversed within one week of a decrease in drug dosage. Further, with no change in drug dosage, the count may stabilize at lower than predrug levels without any clinical sequelae. Predrug platelet counts and frequent platelet counts during therapy are recommended to assist in decisions regarding dosage modifications

Should a platelet count less than 150,000/mm^3 occur, the following actions may be considered:

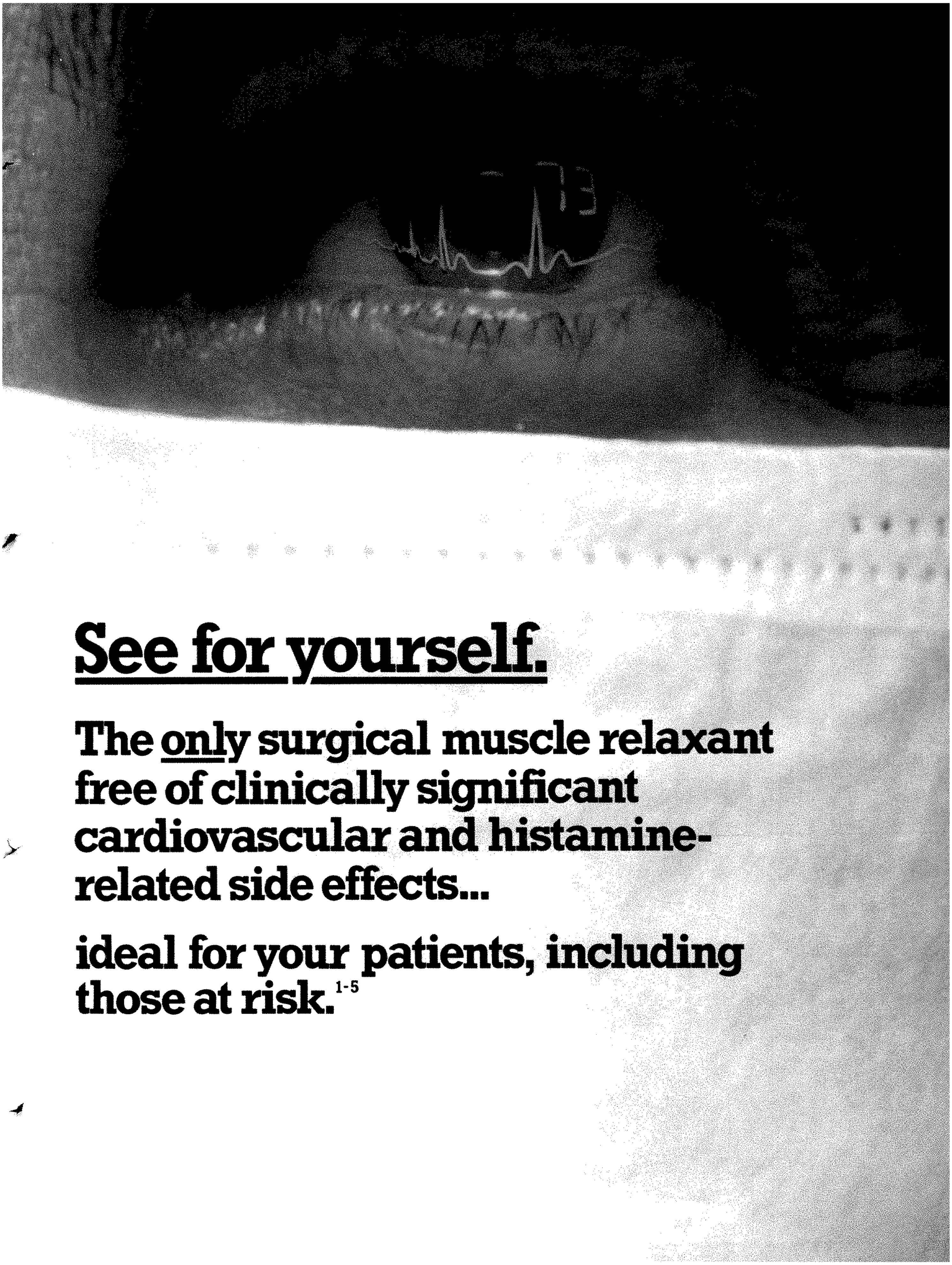
- Maintain total daily dose unchanged, since in some cases counts have either stabilized or returned to pretreatment levels
- Decrease total daily dose.
- Discontinue amrinone if, in the clinical judgment of the physician, risk exceeds the potential benefit.

Gastrointestinal side effects. While gastrointestinal side effects were seen infrequently with IV therapy, should severe or debilitating ones occur, the physician may wish to reduce dosage or discontinue the drug based on the usual benefit-to-risk considerations.

Hepatic toxicity. In clinical experience to date with IV administration, hepatotoxicity has rarely been observed. If acute marked alterations in liver enzymes occur together with clinical symptoms, suggesting an idiosyncratic hypersensitivity reaction, amrinone therapy should be promptly discontinued

If less than marked enzyme alterations occur without clinical symptoms, these nonspecific changes should be evaluated on an individual basis. The clinician may wish to continue amrinone and reduce the dosage or discontinue the drug based on the usual benefit-to-risk considerations

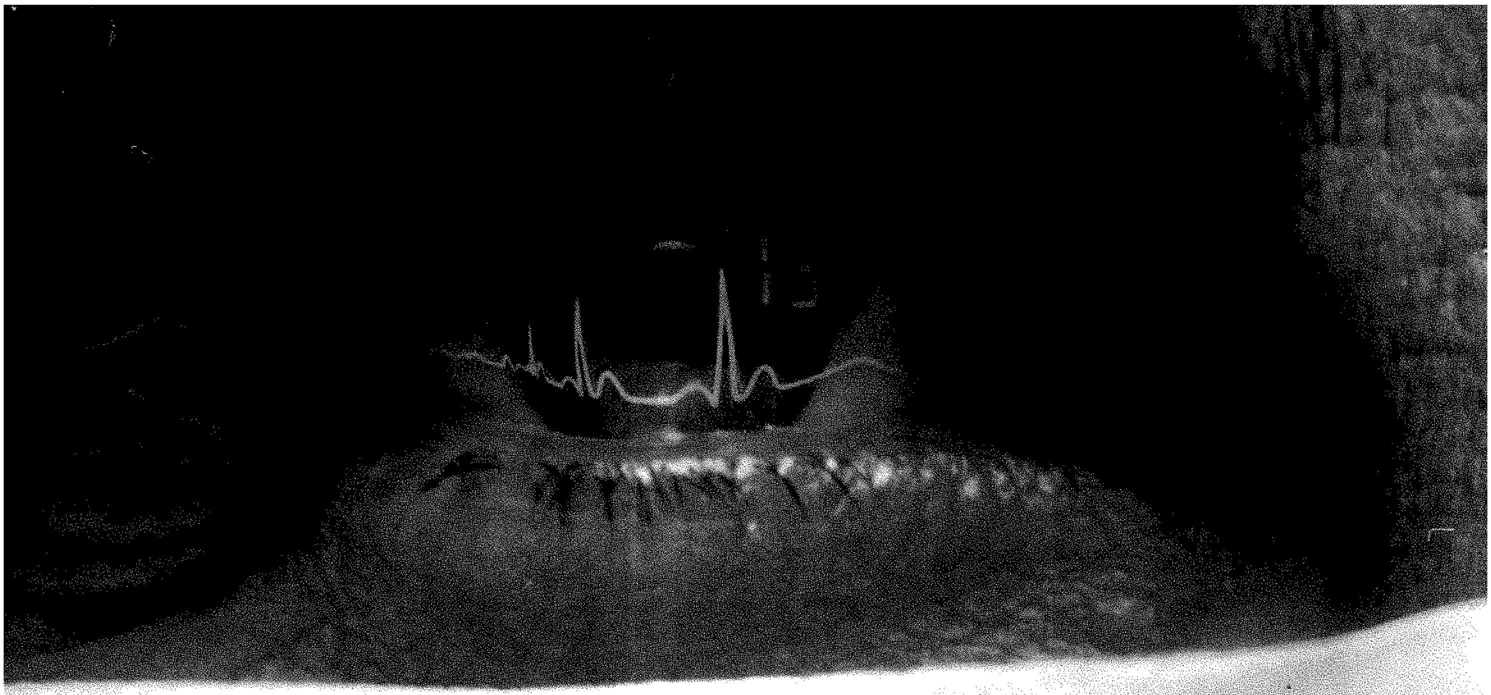
HOW SUPPLIED Ampuls of 20 mL sterile, clear yellow solution containing INOCOR 5 mg/mL, box of 5 (NDC 0024-0888-20) Each 1 mL contains INOCOR lactate equivalent to 5-mg base and 0.25 mg sodium metabisulfite in water for injection



See for yourself.

The only surgical muscle relaxant free of clinically significant cardiovascular and histamine-related side effects...

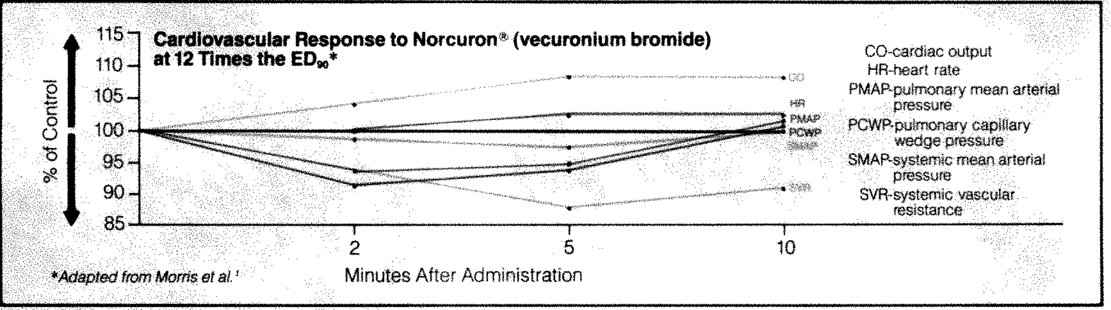
ideal for your patients, including those at risk.[1-5]



See the safety for yourself.

Free of clinically significant cardiovascular effects.*

NORCURON® is the only surgical muscle relaxant for which no clinically significant cardiovascular effects were observed in clinical trials.[1-4] In fact, even at 12 times effective doses, under halothane anesthesia,[1] NORCURON® produced no tachycardia, hypotension, or abnormalities of cardiodynamic function.



Cardiovascular Response to Norcuron® (vecuronium bromide) at 12 Times the ED_{90}*

*Adapted from Morris et al.[1]

Histamine release or histamine-related side effects unlikely to occur...even at 3.5 times the ED_{95}.[5]

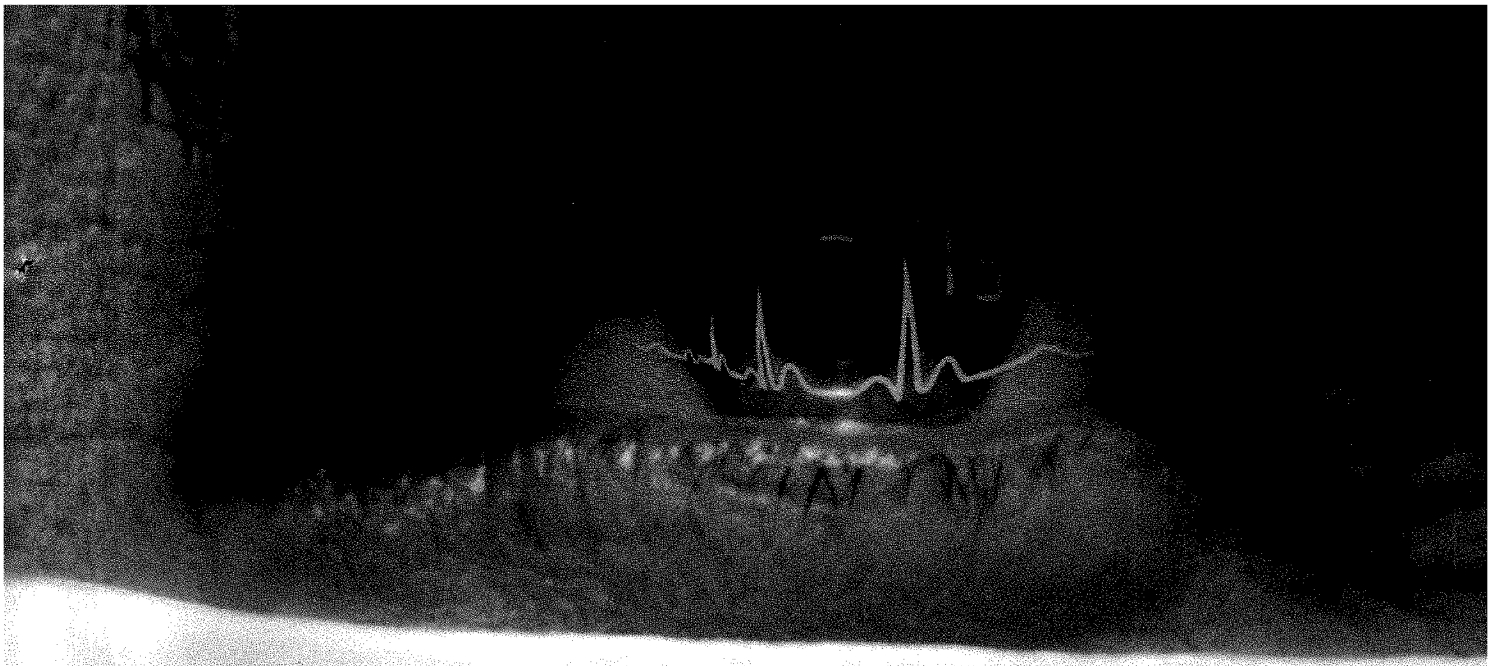
NORCURON® has not been shown to significantly affect circulating histamine, mean arterial blood pressure, and heart rate even in doses at the upper extreme of the recommended clinical range.[5] In contrast, other nondepolarizing neuromuscular blocking agents given at normal clinical doses do increase histamine release to levels at which hypotension and tachycardia tend to occur.[5]

The Effect of Nondepolarizing Muscle Relaxants*

			Percent of Control		
Drug	Dose (mg/kg)	xED_{95}	Histamine	Mean Arterial Pressure	Heart Rate
Tubocurarine	0.5	1	410	78	116
Metocurine	0.5	2	212	79	119
Atracurium	0.6	3	192	80	108
Vecuronium	0.1	1.7	117	100	99
Vecuronium	0.2†	3.5	87	99	102

*Adapted from Basta et al.[5]

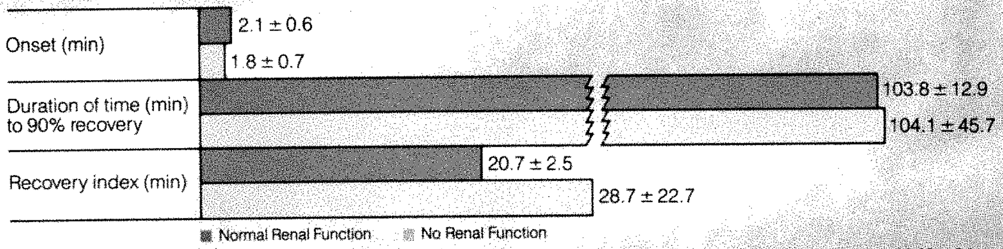
†Although high doses of NORCURON® were used to assess its pharmacokinetics, it is recommended that the initial dose not exceed 0.08 to 0.1 mg/kg.



Performance unaffected by renal function.[6]

Despite administration of high doses of NORCURON®, no significant differences in onset time, duration of action, or recovery index have been noted between patients with and without renal function.[6]

Comparative Indices of Neuromuscular Blockade for Patients With and Without Renal Function Given Equal Doses (0.14 mg/kg)* of NORCURON® (vecuronium bromide) by Bolus Injection†



**Although high doses of NORCURON® were used to assess its pharmacokinetics, it is recommended that the initial dose not exceed 0.08 to 0.1 mg/kg.*

†Adapted from Miller et al.[6]

The surgical muscle relaxant ideal for virtually all patients including those at risk.

Norcuron®

(vecuronium bromide) injection

See full prescribing information on following page.

References: 1. Morris RB, et al: The cardiovascular effects of vecuronium (ORG NC 45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1983; 58:438-440. **2.** Durant NN: Norcuron®—a new nondepolarizing neuromuscular blocking agent. *Semin Anesth* 1982; 1:47-56. **3.** Krieg N, Crul JF, Booij LH: Relative potency of ORG NC 45, pancuronium, alcuronium, and tubocurarine in anesthetized man. *Br J Anaesth* 1980; 52:783-787. **4.** Gallo JA, et al: Hemodynamic effects of bolus injection of vecuronium in cardiac surgical patients. *Anesthesiology* 1984; 61:A63. **5.** Basta SJ, et al: Vecuronium does not alter serum histamine within the clinical dose range. *Anesthesiology* 1983; 59:A273. **6.** Miller RD, et al: Pharmacokinetics of vecuronium in patients with kidney disease, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC 45, Vecuronium Bromide).* Amsterdam, Excerpta Medica, 1983, p 124.

Norcuron® (vecuronium bromide) injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION: NORCURON® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β 3α, 5α, 16β, 17β)-3, 17-bis(acetyloxy)-2-(1-piperidinyl)androstan-16-yl]-1-methyl-, bromide.

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

CLINICAL PHARMACOLOGY: Norcuron® (vecuronium bromide) injection is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about ⅓ more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED_{90} (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® may be decreased by approximately 15% (see DOSAGE AND ADMINISTRATION section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron® is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® (vecuronium bromide) injection has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron®; equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

INDICATIONS AND USAGE: Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation

CONTRAINDICATIONS: None known

WARNINGS: NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: Renal Failure: Norcuron® is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTANT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain theshold or cerebration. Administration must be accompanied by adequate anesthesia.

NO REFRIGERATION REQUIRED

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY). The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Other: Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well-tolerated and produced no adverse reactions during extensive clinic[illegible] trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of t[illegible] drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skel[illegible] muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or a[illegible]

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as [illegible] curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other [illegible] used in anesthetic practice which also cause respiratory depression.

OVERDOSAGE: There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

DOSAGE AND ADMINISTRATION: Norcuron® (vecuronium bromide) injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS)

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution
5% glucose in water
5% glucose in saline
Lactated Ringer's

HOW SUPPLIED: 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 10 (NDC#0052-0442-17).

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STORAGE: PROTECT FROM LIGHT. Store at 15°-30°C (59°-86°F).

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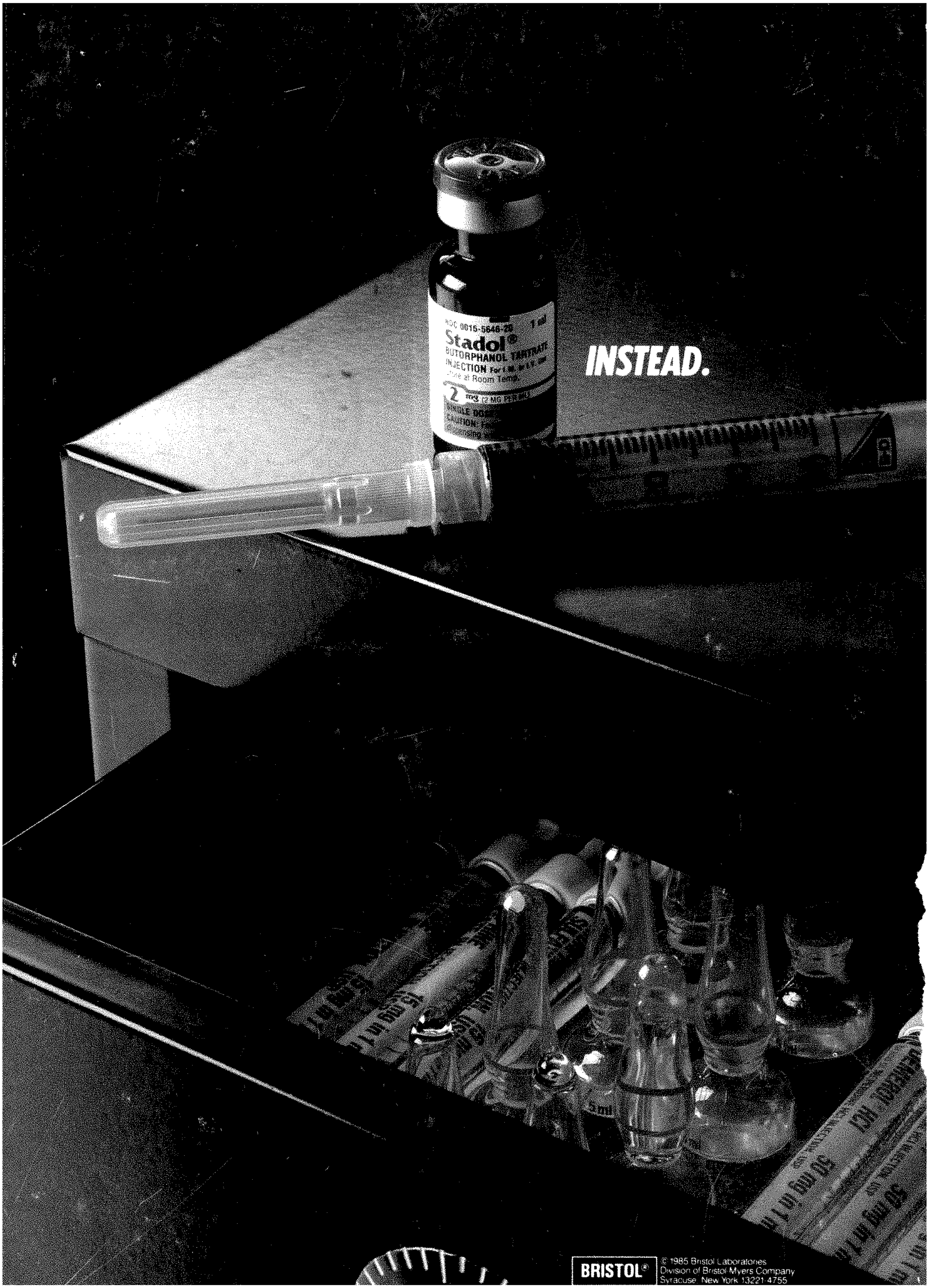

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